IN THE UNITED STATES DISTRICT COURT
FOR THE
DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY, and MANULIFE INSURANCE COMPANY (f\k\a INVESTORS PARTNER INSURANCE COMPANY), Plaintiffs, v. ABBOTT LABORATORIES, Defendant,	CIVIL ACTION NO.05-11150-DPW

AFFIDAVIT OF ALAN FRIEDMAN

I, Alan Friedman, hereby state under oath that;

1. My name is Alan Friedman. I reside in New York, New York.

2. I am a Vice President of CRA International ("CRA"), an economic, financial, and management consulting firm, and head of its Finance Practice in New York. I was engaged by plaintiffs John Hancock Life Insurance Company, John Hancock Variable Life Insurance Company, and Manulife Insurance Company (f/k/a Investors Partner Life Insurance Company) ("John Hancock") and their counsel in 2005 to provide expert analysis and

testimony on the issue of John Hancock's damages arising from its claims against defendant Abbott Laboratories ("Abbott"). This affidavit sets forth my direct testimony. The expert opinions expressed in this affidavit are my own, and all are stated to a reasonable degree of certainty.

3. A brief description of my background is as follows. I have over 25 years of experience in the financial consulting area. I have been retained as an expert witness and/or consultant in over 60 litigation matters and have testified in federal court, arbitrations, and mediations on the subject of damages, including matters involving breach of contract, fraud, financings, acquisitions and intellectual property. In the medical products arena, I have served as an expert witness and/or consultant in cases involving medical devices and pharmaceutical products.

4. CRA is being compensated for my work in this matter at the rate of $550 per hour. I have been assisted in this matter by other CRA personnel who are billed by CRA at rates ranging from $85 to $405 per hour. Neither CRA's compensation, nor my compensation in this matter is dependent on my conclusions or the outcome of the case.

5. In addition to this affidavit, I previously have provided an Expert Report on Damages, dated October 13, 2006, and an Updated Expert Report on Damages ("Updated Report"), dated December 3, 2007. A true and accurate copy of my Updated Report, with my curriculum vitae appended, is attached as PLs' QH. I was also deposed by Abbott's counsel on June 26, 2007.

6. My understanding of the basic underlying facts of this action is as follows.

7. I understand that the terms of the Research Funding Agreement, signed on March 13, 2001 (the "Research Funding Agreement" or the "Agreement"), call for John

Hancock to invest up to $214 million over four years in the development of nine Abbott "Program Compounds". ABT-518, ABT-594 and ABT-773 are three of the Program Compounds included in that Agreement.

8. Under the terms of the Agreement, John Hancock's ability to earn a return on its investment in the Program Compounds depends on the commercial success of those compounds. If some or all of the compounds fail or otherwise are unsuccessful, John Hancock's financial return is reduced accordingly.

9. Similarly, I note that because John Hancock only shares in the revenues generated by the Program Compounds for a set number of years (*i.e.*, until the end of 2015), John Hancock stands to gain more if the Program Compounds are developed quickly.

10. Since the Agreement was executed, I have been informed that the actual condition of, and prospects for, at least three of the Program Compounds, ABT-518, ABT-594 and ABT-773 (the "Misrepresented Compounds"), were materially different from what Abbott represented to John Hancock in the Agreement. I have also been told that Abbott's actual development plans for some of the Program Compounds, including ABT-518 and ABT-594, as of March 13, 2001, were materially different from what Abbott represented to John Hancock in, or at the time of, the Agreement.

11. For the purposes of my analysis I have assumed that Abbott's liability on John Hancock's fraud and breach of contract claims has been established. Specifically, I have assumed that the Court has determined, or will determine, that Abbott breached its obligations to John Hancock under the relevant provisions of the Agreement and further, that Abbott misrepresented or failed to disclose information about the status and prospects for at least the

Misrepresented Compounds, and that those misrepresentations and omissions were material to John Hancock's decision to enter into the Agreement.

12. In order to arrive at my estimation of damages to John Hancock, I reviewed and relied upon numerous documents and information made available to me by counsel for John Hancock. These documents include items such as Abbott's internal valuations of its own pharmaceutical compounds, deposition testimony given in this action by present and former Abbott personnel, internal Abbott e-mails regarding the Misrepresented Compounds, and independent data utilized by Abbott in order to perform internal analyses on its compounds. In addition to the documents made available to me by counsel for John Hancock, I reviewed and relied upon academic literature and various other independent industry sources that relate to the pharmaceutical development process, compound probabilities of success, financial damages valuation, and accounting standards. True and accurate copies of some of these Abbott and industry documents are attached as PLs' ML, MM, ND, NI, NM, PB and RP. A list of the information sources I have considered as part of my work in this matter is appended to my Updated Report, dated December 3, 2007, a true and accurate copy of which is attached as PLs' QH.

13. The five primary components to my damages assessment in this matter are outlined as follows and then discussed in greater detail below:

(A) lost royalty payments to John Hancock relating to the Misrepresented Compounds;

(B) lost milestone payments to John Hancock relating to the Misrepresented Compounds;

(C) damages to John Hancock resulting from Abbott's failure to refund to John Hancock one-third of the unspent portion of the "Aggregate Carryover Amount";

(D) a computation of the amount due to John Hancock in the event of a rescission of the entire Agreement; and

(E) an evaluation of Research Program Spending that potentially would have been forecast, and subsequent John Hancock Program Payments, had all nine of the Program Compounds actually been as viable as represented by Abbott at the time the Agreement was executed.

A. LOST ROYALTY PAYMENTS

14. My first task was to determine the scope of damages related to lost royalty payments to John Hancock. According to the Agreement, John Hancock is entitled to royalty payments on the net sales of the nine Program Compounds by Abbott or any out-licensee; the royalty rate varies from one-half of one percent (0.5%) to eight and one-half percent (8.5%) depending on the level of sales each year. Because the Agreement also specifies that royalties be computed based on the aggregate sales of all nine Program Compounds, my analysis included all nine Program Compounds.

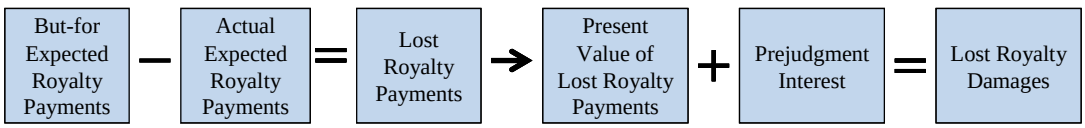
15. In order to compute John Hancock's lost royalty payments, I utilized the "probability-weighted discounted cash flow" approach. This approach often is used by various major pharmaceutical companies – including Abbott – in making their own projections and internal investment decisions regarding new drugs. It is also explicitly recognized and sanctioned by various accounting organizations, including the Financial Accounting Standards

Board (FASB), the United States Office of Management and Budget (OMB), and the American Institute of Certified Public Accountants (AICPA).

16. My computations contrasted the current actual status of the nine Program Compounds (the "Actual Scenario") with the results that reasonably would have occurred if the Misrepresented Compounds actually were as viable as Abbott represented them to be at the time of the Agreement (the "But-for Scenario"). The difference between the Actual Scenario and the But-for Scenario, calculated on a present value basis with the addition of prejudgment interest, constitutes John Hancock's lost royalty payment damages.

17. The following chart represents the overview of my calculation:

Table 1
Lost Royalty Damage Assessment Overview

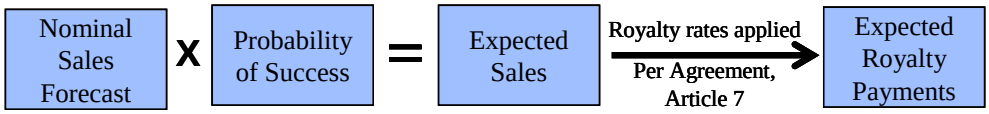


18. It is important to note that the But-for Scenario *did not* assume that the three Misrepresented Compounds would have magically been more successful than they actually were. Rather, the But-for Scenario simply assumed that the condition of, and prospects for, the Misrepresented Compounds were as represented by Abbott at the time of the Agreement. In other words, my analysis assumed only that John Hancock would have received the investment opportunity that it bargained for.

Computation of Expected Royalty Payments – Actual Scenario

19. In computing John Hancock's expected royalty payments in the Actual Scenario, I: (a) determined the appropriate nominal sales forecasts for each of the nine Program Compounds; (b) determined the appropriate probability of success for each of the Program Compounds, (c) computed expected sales; and (d) calculated John Hancock's expected royalty payments based on the aggregated expected sales. This process is illustrated in the following chart:

Table 2
Royalty Payment Computation Overview



Nominal Sales Forecasts – Actual Scenario

20. I obtained my nominal sales forecasts for each of the nine Program Compounds from Abbott itself. These nominal sales forecasts span several years and constitute Abbott's "Low," "Base" and "High Case" forecasted sales of the compound ***assuming*** that technical and regulatory success is achieved. The forecasts were created by Abbott on a compound-by-compound basis, including a ramp-up to, and a decline from, peak sales. Mr. Keith Hendricks, Director of Abbott's Decision Support Group ("DSG"), which analyzed Abbott's research and development investments, has testified under oath on Abbott's behalf that Abbott created these forecasts in the normal course of its business and that Abbott's management actually relied upon them to make Abbott's own project funding decisions. In his deposition, Mr. Hendricks described the comprehensive process by which the DSG compiles

sales forecasts, which includes, among other things, the review of internal and third-party data concerning scientific research and competitive landscapes in both the United States and international (*i.e.*, "ex-US") markets to create commercial sales projections that Abbott deems to be both "reasonable" and "realistic."

21. Table 3, below, shows Abbott's Low, Base, and High Case sales forecasts produced by Abbott at or around the time of the Agreement. Because Abbott's obligation to pay royalty payments to John Hancock ends on December 31, 2015, I have excluded any sales forecast by Abbott after this date:

Table 3
Nominal Sales Forecasts
As of the Agreement Date - March 13, 2001
($ millions)

Program Compound	Low Sales	Base Sales	High Sales
ABT-518	1,193	2,945	5,833
ABT-594	3,970	8,025	14,857
ABT-773	4,739	7,751	12,370
ABT-510	1,783	4,894	8,390
ABT-751	1,207	2,478	4,536
ABT-627	2,518	3,713	6,883
ABT-100	749	2,580	6,653
ABT-492	2,630	4,912	8,405
ABT-724	1,655	4,247	8,495
Total	**20,444**	**41,545**	**76,422**

22. Abbott has terminated its development of eight of the nine Program Compounds. Accordingly, my Actual Scenario only includes Abbott's sales forecast for the one remaining compound - ABT-751. This sales forecast reflects the most current forecast

available from Abbott, dated November 2005, and is less than the original forecast shown above.

Table 4
Nominal Sales Forecasts
Actual Scenario
($ millions)

Program Compound	Low Sales	Base Sales
ABT-751	492	974

23. As shown above, Abbott forecast Low, Base and High Sales amounts for the Program Compounds. While I have reviewed Abbott's High Case sales forecast, and I believe that Abbott created such a forecast because Abbott thought that it had a likelihood of occurring, I have chosen not to compute John Hancock's damages on the basis of Abbott's High Case forecast in the interest of being reasonably conservative in my calculations.

24. I recognize that, although Abbott has terminated its development of all but one of the nine Program Compounds, two of the terminated compounds (ABT-492 and ABT-773) have been out-licensed to third-parties, but not yet approved by the FDA or commercialized. These two out-licensed compounds may, sometime in the future, generate royalties or milestone payments that would reduce John Hancock's damages. However, due to a lack of information from Abbott or its licensees pertaining to these out-licensed compounds, I have assumed for purposes of my present analysis that John Hancock will not receive actual royalties or milestone payments on those compounds. I can and will modify my analysis in this regard if additional information becomes available or circumstances change prior to trial, or if requested by the Court.

Probability of Success – Actual Scenario

25. Abbott's sales forecasts represent nominal sales, or sales that are expected to be made assuming that the compound successfully passes all of the technical and regulatory hurdles required for market launch. As the second step in my analysis, I adjusted those nominal sales to reflect the risk that these compounds would not successfully pass those hurdles.

26. As mentioned in Paragraph 15 above, the idea of adjusting nominal sales forecasts for risk is not a novel concept. In the pharmaceutical industry generally, and with respect to this case in particular, risks associated with technical and regulatory issues can be accounted for on a compound-by-compound basis using "probabilities of success" or "success rates". A "probability of success" refers to the probability that a compound will successfully overcome all necessary technical and regulatory hurdles on its way to market. Abbott and third-party researchers frequently estimate probabilities of success not only for specific compounds, but also for each indication (or disease) a compound is proposed to treat and a compound's probability of passing through each phase of development. The FASB refers to the process of accounting for risk by applying a probability of success to a potential outcome as the "Expected Cash Flow" approach because it applies "specific assumptions about the range of cash flows and their respective probabilities."

27. It is important to note that a low probability of success, however, does not imply that a compound has no measurable value. This view is supported by the AICPA in its guidelines governing the fair value of "Assets Acquired in a Business Combination to be Used in Research and Development Activities," which state, in part, that: "low probability of success is not evidence, by itself, that the resulting estimate of fair value is not reasonably reliable."

28. I considered various sources to identify the appropriate probabilities of success for the Program Compounds. They included those created internally at Abbott and those created by independent, third parties. For my Base Case analysis I chose Abbott's own internal probabilities of success because these forecasts were customized by Abbott for each specific Program Compound (Table 5). For my Low Case, I chose the set of publicly-available industry success rates, published by the Center for Medicines Research International ("CMR International"), that represent the lowest combined probabilities of success for the Program Compounds (Table 6).

Table 5
Compound Probabilities of Success
Company Projected by Compound/Indication

Program Compound	Therapy (Indication)	Stage of Development	BASE CASE Abbott Projected	Abbott Historical
Misrepresented Program Compounds (As of Agreement Date: March 13, 2001)				
ABT-518	Anticancer (All)	Phase I	13%	21%
ABT-594	Analgesic (Chron Pain)	Phase II	16%	38%
ABT-594	Analgesic (Neuro Pain)	Phase II	32%	38%
ABT-594	Analgesic (Noci Pain)	Phase II	8%	38%
ABT-773	Anti-Infective (Tablet)	Phase III	72%	67%
ABT-773	Anti-Infective (IV)	Phase I	36%	21%
ABT-773	Anti-Infective (Japan)	Phase I	37%	21%
Other Program Compounds (As of Most Recent Forecast: ~December 2005)				
ABT-510	Anticancer (NonSarc)	Phase II	12%	38%
ABT-751	Anticancer (All)	Phase II	41%	38%
ABT-627	Anticancer (NonPCA)	Phase II	13%	38%
ABT-627	Anticancer (HRPCA)	Phase III	35%	67%
ABT-627	Anticancer (Japan)	Phase I	14%	21%
ABT-627	Anticancer (IV)	Phase IV	35%	n/a
ABT-100	Anticancer (All)	Terminated	0%	0%
ABT-724	MED (All)	Terminated	0%	0%
ABT-492	Anti-Infective (All)	Terminated	0%	0%

Table 6

Compound Probabilities of Success
Industry Projected by Compound/Indication

Program Compound	Therapy (Indication)	Stage of Development	LOW CASE CMR International (2004)	Pharma Predict (2006)	DiMasi (1995)	DiMasi (2001)
Misrepresented Program Compounds (As of Agreement Date: March 13, 2001)						
ABT-518	Anticancer (All)	Phase I	6%	23%	23%	22%
ABT-594	Analgesic (Chron Pain)	Phase II	17%	26%	31%	30%
ABT-594	Analgesic (Neuro Pain)	Phase II	17%	26%	31%	30%
ABT-594	Analgesic (Noci Pain)	Phase II	17%	26%	31%	30%
ABT-773	Anti-Infective (Tablet)	Phase III	75%	84%	77%	69%
ABT-773	Anti-Infective (IV)	Phase I	33%	50%	30%	22%
ABT-773	Anti-Infective (Japan)	Phase I	33%	50%	30%	22%
Other Program Compounds (As of Most Recent Forecast: ~December 2005)						
ABT-510	Anticancer (NonSarc)	Phase II	8%	35%	31%	30%
ABT-751	Anticancer (All)	Phase II	8%	35%	31%	30%
ABT-627	Anticancer (NonPCA)	Phase II	8%	35%	31%	30%
ABT-627	Anticancer (HRPCA)	Phase III	32%	67%	63%	69%
ABT-627	Anticancer (Japan)	Phase I	6%	23%	23%	22%
ABT-627	Anticancer (IV)	Phase IV	35%	n/a	n/a	n/a
ABT-100	Anticancer (All)	Terminated	0%	0%	0%	0%
ABT-724	MED (All)	Terminated	0%	0%	0%	0%
ABT-492	Anti-Infective (All)	Terminated	0%	0%	0%	0%

Computing Expected Sales – Actual Scenario

29. The next step in my computation of John Hancock's lost royalty payments was to compute expected sales. I multiplied Abbott's Low Case nominal sales forecast by the Low Case (CMR International) probabilities of success for each Program Compound and indication to produce Low Case expected sales. To compute the Base Case expected sales, I multiplied Abbott's Base Case nominal sales forecast by Abbott's forecast probability of success by Program Compound and by indication. This was a straight-forward mathematical exercise. Table 7 summarizes my calculated Low and Base Case expected sales for the Actual

Scenario. I have included only ABT-751 in this calculation because it is the only compound still under development by Abbott at this time.

Table 7
Expected Sales
Actual Scenario
($ millions)

Program Compound	Low Case	Base Case
ABT-751	39	399

Computing Expected Royalty Payments – Actual Scenario

30. The fourth step in my lost royalty payment analysis was to compute John Hancock's expected royalty payments. To calculate those payments, I applied the royalty rates and terms contained in Article 7.1 of the Agreement, which stipulate that royalties are to be paid to John Hancock by Abbott, or its out-licensees, as a percentage of aggregate sales for all Program Compounds. The royalty rate paid to John Hancock diminishes in specified tiers as aggregate, annual sales increase. For example, Abbott and/or its out-licensees must pay royalties to John Hancock at a rate of eight and one-half percent (8.5%) on the first $400 million of aggregate, annual sales of the Program Compounds. The royalty rate decreases to four percent (4%) for aggregate sales of the Program Compounds in any year in which sales total between $400 million and $1 billion.

31. Article 7.2 of the Agreement further provides that Abbott and/or its licensees must pay royalties to John Hancock only on the first ten (10) years of a Program Compound's sales. This limitation on Hancock's royalty rights is in addition to the termination of the royalty payment obligation on December 31, 2015 (*See* Paragraph 21). Table 8 summarizes

the calculation of John Hancock's expected royalty payments in the Actual Scenario, including, as appropriate, an adjustment for the ten (10) year royalty payment limit:

Table 8
Expected Royalty Payments
Actual Scenario
($ millions)

Item	Low Case	Base Case
Aggregate Expected Sales	39	399
- Sales Reduction for 10-year Limit	-	-
Aggregate Expected Sales after Reduction	39	399
* 8.5% of Yearly Net Sales up to $400M	3	34
* 4.0% of Yearly Net Sales in excess of $400M up to $1B	-	-
* 1.0% of Yearly Net Sales in excess of $1B up to $2B	-	-
* 0.5% of Yearly Net Sales in excess of $2B	-	-
Total Expected Royalty Payments	**3**	**34**

32. Based on the above, I have concluded that John Hancock reasonably can expect to receive royalty payments from Abbott resulting from the sales of the only Program Compound remaining (ABT-751) ranging from approximately $3 million to approximately $34 million through the year 2015.

Computation of Expected Royalty Payments – But-for Scenario

33. The next step in my damage analysis was to calculate John Hancock's expected royalty payments in the But-for Scenario. In order to perform that calculation, I repeated the four steps described in Paragraph 19, above. In my But-for Scenario, I assumed that the three Misrepresented Compounds had the condition and prospects that were represented by Abbott at the time the Agreement was executed in March 2001, and therefore the associated sales forecasts and probabilities of success for those compounds as well. My

assumptions relating to the remaining six Program Compounds were the same as in the Actual Scenario.

Sales Forecasts – But-for Scenario

34. For the Misrepresented Compounds, I utilized the sales forecast data produced by Abbott nearest to the March 13, 2001 Agreement date, but before Abbott decided to cease development of the Misrepresented Compounds. As noted above, sales forecasts for the other Program Compounds are the same as in the Actual Scenario. Nominal sales forecasts utilized in the But-for Scenario are shown in Table 9:

Table 9
Nominal Sales Forecasts
But-for Scenario
($ millions)

Program Compound	Low Sales	Base Sales
ABT-518	1,193	2,945
ABT-594	3,970	8,025
ABT-773	4,739	7,751
ABT-510	-	-
ABT-751	492	974
ABT-627	-	-
ABT-100	-	-
ABT-492	-	-
ABT-724	-	-
Total	**10,394**	**19,695**

Success Rates – But-for Scenario

35. The next step in my But-for Scenario calculation was to select the appropriate probability of success data to use in the But-for computation of royalty damages. Once again, I used Abbott's probabilities of success for the Base Case and the CMR International

probabilities of success for the Low Case. As noted above, the success rates that I used for ABT-751 are the same as those that I used in my Actual Scenario calculations and applied by Program Compound and by indication.

Computing Expected Sales – But-for Scenario

36. The next step in my But-for Scenario calculation was to compute expected sales for the Program Compounds by multiplying the nominal sales forecast by the probabilities of success for each Program Compound and indication. The calculated expected sales for the four relevant Program Compounds are presented in Table 10:

Table 10
Expected Sales
But-for Scenario
($ millions)

Program Compound	Low Case	Base Case
ABT-518	72	368
ABT-594	675	2,194
ABT-773	3,033	4,921
ABT-510	-	-
ABT-751	39	399
ABT-627	-	-
ABT-100	-	-
ABT-492	-	-
ABT-724	-	-
Total	**3,818**	**7,882**

Computing Expected Royalty Payments – But-for Scenario

37. The last step in my But-for Scenario calculation was to compute John Hancock's expected royalty payments. As described in Paragraph 30, above, I applied the royalty terms and rates contained in Article 7.1 of the Agreement, which stipulate that the annual royalties to be paid to John Hancock by Abbott or its out-licensees are calculated as a

percentage of aggregate sales for all of the Program Compounds. The results of my calculation of John Hancock's expected royalty payments in the But-for Scenario are shown in Table 11:

Table 11
Expected Royalty Payments
But-for Scenario
($ millions)

Item	Low Case	Base Case
Aggregate Expected Sales	3,818	7,882
- Sales Reduction for 10-year Limit	938	1,744
Aggregate Expected Sales after Reduction	2,880	6,138
* 8.5% of Yearly Net Sales up to $400M	245	337
* 4.0% of Yearly Net Sales in excess of $400M up to $1B	0.1	87
* 1.0% of Yearly Net Sales in excess of $1B up to $2B	-	-
* 0.5% of Yearly Net Sales in excess of $2B	-	-
Total Expected Royalty Payments	**245**	**424**

38. Based on the above, I have concluded that John Hancock reasonably could have expected to receive royalty payments in the But-for Scenario ranging from approximately $245 million (Low Case) to approximately $424 million (Base Case) through the year 2015.

Computing John Hancock's Lost Royalty Payments

39. The lost royalty payments sustained by John Hancock equal the difference between the But-for Scenario royalty payments and the Actual Scenario royalty payments.

40. Because John Hancock's lost royalty payments would have been received over a number of years, I discounted all future royalty payments by the United States Treasury Rate of 4.04% to reflect a present value of royalty payments as of December 31, 2007. I selected a 'risk-free' discount rate to avoid duplicating the discount factors that already are reflected in the success probabilities and sales forecasts that I used in calculating expected

royalties. This approach to discounting cash flows is consistent with, and specifically illustrated in, AICPA guidelines governing the fair value of "Assets Acquired in a Business Combination to be Used in Research and Development Activities." A summary of the present value calculation and John Hancock's lost royalty payments are presented in Table 12 and Table 13:

Table 12
Present Value Computation
Base Case Lost Royalties
($ millions)

Item	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals
But-for Expected Royalty Payments	1	12	23	35	41	47	50	51	50	51	34	17	12	424
- Actual Expected Royalty Payments	-	-	-	-	-	-	0	1	1	4	9	11	7	34
Lost Royalty Payments - Nominal	**1**	**12**	**23**	**35**	**41**	**47**	**50**	**50**	**49**	**47**	**25**	**5**	**5**	**390**
* Present Value Factor for Future Damages (Discount Rate = 4.04%)	1	1	1	1	1.00	0.96	0.92	0.89	0.85	0.82	0.79	0.76	0.73	
Present Value of Lost Royalty Payments	**1**	**12**	**23**	**35**	**41**	**45**	**46**	**44**	**42**	**38**	**20**	**4**	**4**	**355**

Table 13
Present Value Computation
Low Case Lost Royalties
($ millions)

Item	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals
But-for Expected Royalty Payments	1	7	14	19	26	32	34	34	34	33	8	2	2	245
- Actual Expected Royalty Payments	-	-	-	-	-	-	0	0	0	0	1	1	1	3
Lost Royalty Payments - Nominal	**1**	**7**	**14**	**19**	**26**	**32**	**34**	**34**	**33**	**32**	**7**	**1**	**1**	**241**
* Present Value Factor for Future Damages (Discount Rate = 4.04%)	1	1	1	1	1.00	0.96	0.92	0.89	0.85	0.82	0.79	0.76	0.73	
Present Value of Lost Royalty Payments	**1**	**7**	**14**	**19**	**26**	**31**	**31**	**30**	**29**	**26**	**6**	**1**	**1**	**221**

41. Based on the above, I have concluded that John Hancock sustained lost royalty payments ranging from approximately $221 million (Low Case) to approximately $355 million (Base Case).

42. I also computed prejudgment interest on all of the royalty payments that John Hancock would have received prior to December 31, 2007 in the But-for Scenario. For this calculation I applied Illinois' standard statutory prejudgment interest rate of five percent (5%) to John Hancock's lost royalty payments. Prejudgment interest on the lost royalty payments ranges from approximately $4 million (Low Case) to approximately $6 million (Base Case).

43. Table 14 summarizes John Hancock's total lost royalty damages, as computed above, including prejudgment interest:

Table 14
Lost Royalty Damage Assessment Overview

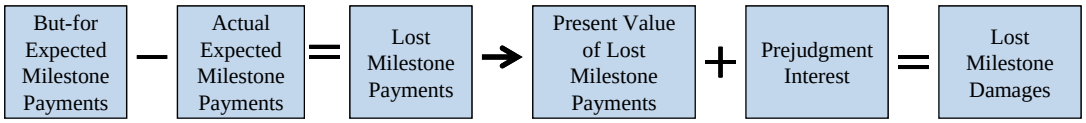
	But-for Expected Royalty Payments	–	Actual Expected Royalty Payments	=	Lost Royalties Payments	→	Present Value of Lost Royalty Payments	+	Prejudgment Interest	=	Lost Royalty Damages
Low Case	$245M	–	$3M	=	$241M	→	$221M	+	$4M	=	**$225M**
Base Case	$424M	–	$34M	=	$390M	→	$355M	+	$6M	=	**$361M**

B. LOST MILESTONE DAMAGES

44. According to the terms of the Agreement, Abbott or its out-licensees are required to make a $20 million milestone payment to John Hancock if and when the first Program Compound achieves regulatory approval by the Food and Drug Administration ("FDA"). Abbott or its out-licensees also are required to make $10 million milestone payments to John Hancock for each subsequent Program Compound that receives approval by the FDA. The Agreement caps John Hancock's total milestone payments at $40 million.

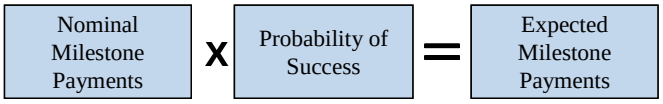
45. Therefore, the second component to my damage analysis was to determine John Hancock's lost milestone payments. To compute these damages, I undertook essentially the same steps explained above in my royalty damages calculation. Specifically, I compared the value of expected milestone payments in the But-for Scenario with the value of expected milestone payments in the Actual Scenario. The model and methodology for computing these damages is depicted in Table 15:

Table 15
Lost Milestone Damage Assessment Overview



46. In order to compute John Hancock's expected milestone payments in the Actual Scenario, I: (a) determined the appropriate nominal milestone payments and their timing relating to the nine Program Compounds; (b) determined the appropriate probability of success for each Program Compound; and (c) computed John Hancock's expected milestone payments. This process is illustrated in Table 16:

Table 16
Milestone Payment Computation Overview



Nominal Milestone Payments – Actual Scenario

47. My first step in determining John Hancock's expected milestone payments in the Actual Scenario was to assign nominal FDA Milestone payments to each Program Compound, assuming that each Compound has survived its technical and regulatory hurdles.

48. Using the schedule of anticipated Program Compound launch dates that Abbott represented to John Hancock in the Agreement, I assigned nominal milestone payments to the Program Compounds. In the Actual Scenario, ABT-751 is the only remaining compound. Therefore, I assigned that Program Compound a milestone payment of $20 million. This value applies equally to both the Base Case and Low Case calculations because the nominal milestone payment obligations are the same in both.

Success Rates – Actual Scenario

49. The next step in determining John Hancock's expected milestone payments in the Actual Scenario was to account for technical and regulatory risk factors associated with the Program Compounds. Consistent with my analysis with respect to John Hancock's lost royalty payments, my Base Case analysis utilized Abbott's own internal probabilities of success for the individual Program Compounds (Table 5), and my Low Case analysis utilized the CMR International probabilities of success (Table 6). Because I calculated the Actual Scenario based on the performance to date of the nine Program Compounds, my analysis in this regard is limited to ABT-751, which is the only Program Compound still being developed by Abbott.

Computation of Expected Milestone Payments – Actual Scenario

50. The next step in determining John Hancock's expected milestone payments in the Actual Scenario was to compute the expected milestone payments by multiplying the nominal milestone payments and the probabilities of success for each compound. Again, this was a straight-forward mathematical exercise. Computed as described, John Hancock's expected milestone payments in the Actual Scenario range from approximately $2 million (Low Case) to approximately $8 million (Base Case).

Nominal Milestone Payments – But-for Scenario

51. The next step in my damage analysis was to calculate John Hancock's expected milestone payments in the But-for Scenario. I first identified the nominal milestone payments. Using the schedule of anticipated Program Compound launch dates that Abbott represented to John Hancock in the Agreement, I assigned nominal milestone payments to the Program Compounds. In the But-for Scenario, four Program Compounds (ABT-751, ABT-773, ABT-594 and ABT-518) remain. I assigned a milestone payment of $20 to the first compound expected to launch, and additional milestone payments of $10 million to two subsequent Program Compounds, recognizing that the Agreement imposes a $40 million cap on John Hancock's total milestone payments. These values apply equally to the Base Case and Low Case calculations because the nominal milestone payment obligations are the same in both cases.

Success Rates – But-for Scenario

52. The next step in my calculation of John Hancock's expected milestone payments in the But-for Scenario was to determine the appropriate probabilities of success to be used in the But-for milestone payment computation. Consistent with my analysis of John Hancock's Actual and But-for royalty payment scenarios and the Actual milestone scenario noted above, I utilized Abbott's own internal probabilities of success for the individual Program Compounds for my Base Case analysis (Table 5), and the CMR International probabilities of success for my Low Case analysis (Table 6).

Computation of Expected Milestone Payments – But-for Scenario

53. The next step in my calculation of John Hancock's expected milestone payments in the But-for Scenario was to compute expected milestone payments by multiplying

the nominal milestone payments for each Program Compound by their respective probabilities of success. My calculations establish that John Hancock's total expected milestone payments in the But-for Scenario are between approximately $18 million (Low Case) and approximately $21 million (Base Case).

Computing Lost Milestone Payments and Damages

54. The lost milestone payments sustained by John Hancock are the difference between the But-for Scenario expected milestone payments and the Actual Scenario expected milestone payments.

55. To determine the present value of John Hancock's lost milestone payments, I discounted all future royalty payments by applying the same 'risk-free' discount rate (the United States Treasury Rate of 4.04%) that I previously used in determining the present value of John Hancock's lost royalty payments.

56. Based on the above, I have concluded that John Hancock has sustained lost milestone payments ranging from approximately $13 million (Base Case) to approximately $17 million (Low Case).

57. I also computed prejudgment interest on John Hancock's lost milestone damage estimates by applying Illinois' standard statutory prejudgment interest rate of five percent (5%) to the lost milestone payments. Prejudgment interest on those lost milestone payments ranges from approximately $2.6 million (Base Case) to approximately $2.7 million (Low Case).

58. Table 17 summarizes John Hancock's total lost milestone payment damages computed above, including prejudgment interest:

Table 17

Lost Milestone Damage Assessment Overview

	But-for Expected Milestone Payments		Actual Expected Milestone Payments	=	Lost Milestone Payments	→	Present Value of Lost Milestone Payments	+	Prejudgment Interest	=	Lost Milestone Damages
Low Case	$18M	–	$2M	=	$17M	→	$17M	+	$3M	=	**$19M**
Base Case	$21M	–	$8M	=	$13M	→	$13M	+	$3M	=	**$16M**

Differences due to Rounding

C. PROGRAM SPENDING DAMAGES

59. I understand that the Agreement states that Abbott was obligated to spend at least $614 million (the "Aggregate Spending Target") on costs associated with the research and development of the Program Compounds ("Program Related Costs") during the four-year "Program Term," which began on March 13, 2001 and ended on December 31, 2004. I further understand that if Abbott failed to reach the Aggregate Spending Target within the four-year Program Term, Abbott had one additional year (*i.e.*, 2005) to spend the remaining portion of the Aggregate Spending Target (the "Aggregate Carryover Amount"). Section 3.3(b) of the Agreement requires Abbott to refund to John Hancock one-third of the portion of the Aggregate Carryover Amount that remained unspent at the end of 2005 (referred to herein as the "Spending Shortfall").

60. It is my understanding that a Spending Shortfall occurred, and that Abbott has not made any payments to John Hancock on account of that Spending Shortfall. Accordingly, the third component to my damage analysis was to determine John Hancock's damages resulting from Abbott's breach of its obligation to make the refund payment required under Section 3.3(b).

61. According to my understanding of the Agreement, Abbott also was required to provide John Hancock with "Annual Research Plans," which were to include Abbott's historical, actual spending throughout the Program Term. In my initial damages report, I relied upon Abbott's 2006 Annual Research Plan in order to determine whether Abbott had fulfilled its program spending obligations. In that report, I calculated the Spending Shortfall to be $65.4 million.

62. Since I prepared my initial Report, Abbott has purported to revise its historical, actual spending on Program Related Costs on multiple occasions. I have re-calculated the Spending Shortfall using the two most recent accounts of Program Spending produced by Abbott in *Abbott's Amended Responses and Objections to John Hancock's 2nd Set of Interrogatories*, dated August 3, 2007 ("Abbott's Amended Responses"), and Abbott's 2008 Research Funding Plan Update, dated November 20, 2007 (the "2008 Plan Update").

63. In Abbott's Amended Responses, Abbott claims that its actual spending on Program Related Costs during the relevant period was $529 million. The Aggregate Carryover Amount was, therefore, $85 million (*i.e.*, $614 million minus $529 million). One-third of that amount is approximately $28 million.

64. Conversely, in Abbott's 2008 Plan Update, Abbott reported to John Hancock that its actual spending on Program Related Costs during the four-year Program Term was $515 million. The Aggregate Carryover Amount was, therefore, $99 million (*i.e.*, $614 million minus $515 million). One-third of that amount is approximately $33 million.

65. Because Abbott failed to spend the full Aggregate Carryover Amount by the end of 2005, I understand that Section 3.3(b) of the Agreement requires Abbott to refund to John Hancock one-third of the resulting Spending Shortfall. Depending on which set of

Abbott numbers are correct, John Hancock's damages are either $28 million (Abbott's Amended Responses) or $33 million (Abbott's more recent 2008 Plan Update). Applying the Illinois standard statutory prejudgment interest rate of five percent (5%), John Hancock's prejudgment interest on one-third of the Spending Shortfall is either $2.8 million (Abbott's Amended Responses) or $3.2 million (Abbott's more recent 2008 Plan Update). Table 18 summarizes my calculation of John Hancock's damages using both sets of spending numbers, including prejudgment interest:

Table 18
Calculation of Abbott's Aggregate Spending Shortfall
($ millions)

Item	Response to 2nd Set of Interrogatories	2008 Research Funding Plan Update
Aggregate Spending Target	614.0	614.0
- Actual Aggregate Spending During Program Term (2001 - 2004)	456.2	442.0
Aggregate Carryover Amount	157.8	172.0
- Actual 2005 Spending	73.0	72.9
Unspent Aggregate Carryover Amount	84.8	99.1
1/3 of Unspent Aggregate Carryover Amount	**28.3**	**33.0**
Prejudgment Interest	**2.8**	**3.2**
Total	**31.0**	**36.3**

D. RESCISSION COMPUTATION

66. For the fourth component of my damages analysis, I considered the possibility that, as an alternative remedy in this case, John Hancock may elect to request that the Court rescind the Research Funding Agreement in its entirety. I therefore have computed damages that would be owed to John Hancock if the Agreement is rescinded, and the parties are to be

put back in the financial position they would have been in had they never entered into the Agreement.

67. John Hancock's Rescission Damages are equal to John Hancock's total Program Payments to Abbott, minus any management fees or milestone payments that Abbott paid to John Hancock under the Agreement, plus prejudgment interest (to compensate John Hancock for the time value of the funds while they remained in Abbott's possession) if the Court so directs. The net amount of John Hancock's Program Payments, minus management fees and milestone payments received to date, is approximately $89.6 million. Applying Illinois' standard statutory prejudgment interest rate of five percent (5%), John Hancock's prejudgment interest on Rescission Damages is approximately $28.4 million. Table 19 summarizes my Rescission Damages calculation:

Table 19
Calculation of Agreement Rescission Amount
($ millions)

Item	2001	2002	2003	2004	2005	2006	2007	Total
John Hancock Payments to Abbott:								
Program Payments	50.0	54.0	-	-	-	-	-	104.0
Abbott Payments to John Hancock:								
Management Fees	-	(2.0)	(2.0)	(2.0)	-	-	-	(6.0)
Milestone Payments	-	(8.0)	-	-	-	-	-	(8.0)
Wakunuga Licensing (ABT-492)	-	-	-	-	-	-	(0.4)	(0.4)
Rescission Payment	50.0	44.0	(2.0)	(2.0)	-	-	(0.4)	**89.6**
Prejudgment Interest	-	2.5	4.8	5.0	5.1	5.4	5.6	**28.4**
Total	**50.0**	**46.5**	**2.8**	**3.0**	**5.1**	**5.4**	**5.2**	**118.0**

E. BUT-FOR SCENARIO PROGRAM SPENDING

68. For the fifth component of my damages analysis, I examined the Program Related Costs that Abbott might have intended and reasonably expected to spend in the But-for Scenario had the portfolio of Program Compounds actually been comprised of nine compounds as viable as represented by Abbott. This component, if applicable, would reduce John Hancock's overall damages by potentially triggering additional Program Payments on Hancock's part. My analysis in this regard is set out in Exhibits 9.1 to 9.4 of my Updated Report (PLs' QH).

69. Under the terms of the Agreement, I understand that Abbott was required to submit Annual Spending Plans that forecasted Abbott's intended and reasonably expected aggregate spending on Program Related Costs of at least $614 million during the four-year Program Term, which began on March 13, 2001 and ended on December 31, 2004. I further understand that the Agreement requires that, if Abbott ever failed to demonstrate that it intended and reasonably expected to spend less than $614 million over that period, John Hancock's obligation to make additional Program Payments for any subsequent Program Years would automatically terminate.

70. The United States District Court and the U.S. Court of Appeals previously have ruled in prior litigation between the parties that Abbott actually failed to demonstrate in 2002 its intention and reasonable expectation to spend at least $614 million on Program Related Costs over the four-year Program Term, with the result that John Hancock's obligation to make its third and fourth Program Payments for 2003 and 2004, respectively, automatically terminated at that time. I appreciate, however, that the Misrepresented Compounds already had been terminated by the time Abbott prepared its spending forecast in 2002, and that

continued development of the Misrepresented Compounds, as contemplated in my But-for Scenario, might have caused Abbott to forecast total expected spending over the Program Term in excess of $614 million, thereby triggering additional Program Payments on John Hancock's part.

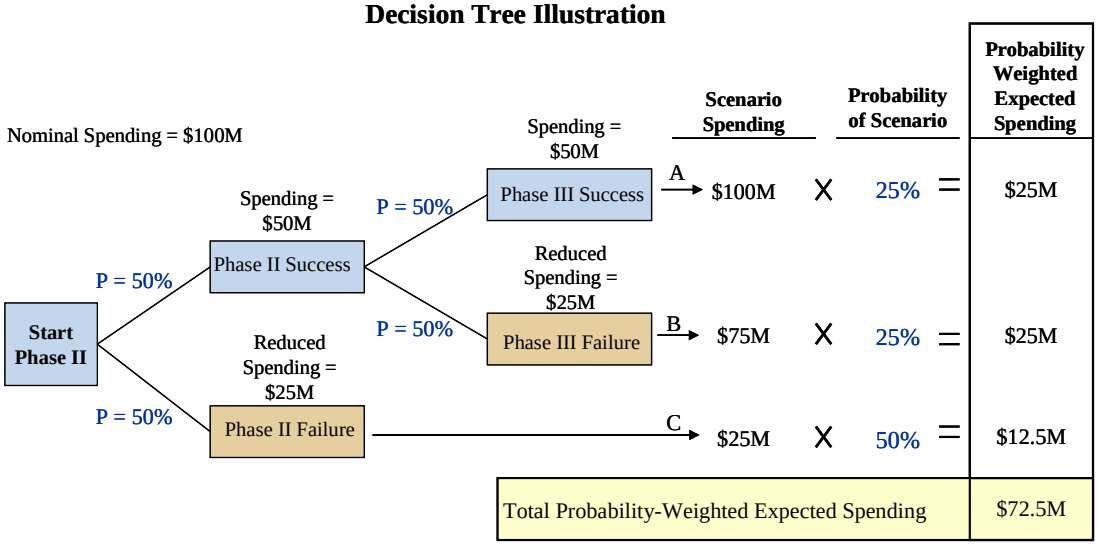
71. In order to determine Abbott's intended and reasonably expected spending on Program Related Costs in the But-for Scenario, I started with Abbott's actual and projected spending from Abbott's own Annual Research Plans. For the six compounds not at issue, the actual and projected spending from Abbott in the 2003 and 2004 Annual Research Plans was maintained throughout my calculations, subject to the modifications described in Paragraphs 75 and 76, below. For the Misrepresented Compounds, I calculated Abbott's future reasonably intended and expected spending for each compound using a decision-tree analysis that incorporates the nominal spending projections that Abbott represented to John Hancock in the Agreement, and the same success probabilities that I utilized for the purpose of calculating John Hancock's lost royalty and milestone payments in my Base Case and Low Case analyses.

72. Decision trees are common quantitative techniques whereby various alternative outcomes are considered based on related conditions of risk and success. In this case the decision tree maps various compound spending forecasts that could occur as a compound goes through various stages of development and either achieves success or meets failure.

73. An illustrative example of the decision tree approach and the expected spending calculation is shown in Table 20, below. In this illustration, I computed expected spending on a hypothetical compound. In this case, the compound is beginning Phase II and has a fifty percent (50%) probability of completing Phase II, and if successful, a fifty percent (50%) probability of completing Phase III. I assumed that the projected cost of Phase II, if

completed, is $50 million, and the projected cost of Phase III, if completed, is another $50 million. I further assumed that, if the compound fails during a phase, only one-half of the projected spending will occur. There are three possible outcomes in this hypothetical example: (A) the compound successfully completes Phase II and Phase III, resulting in total spending of $100 million; (B) the compound is successful in Phase II, but fails in Phase III, resulting in total spending of $75 million; and (C) the compound fails in Phase II and never enters Phase III, resulting in total spending of $25 million. The probability of scenario A is *50% X 50% = 25%*; the probability of scenario B is *50% X 50% = 25%*; and the probability of scenario C is *50%*. By applying these probabilities to the dollar spending amounts in each scenario, and summing them, the expected probability-weighted spending in this illustration is $72.5 million.

Table 20
Decision Tree Illustration



74. In contrast, if in the above illustration, I had merely forecast spending assuming success in both phases, I would have forecast spending of $100 million. This 'one hundred percent success' approach is equivalent to the nominal forecast provided to John Hancock by Abbott, and does not fairly reflect a "reasonably expected" forecast.

75. There are two related issues with respect to Abbott's actual spending that are important to note in this context. First, the testimony of Mr. Keith Hendricks' of Abbott establishes that Abbott's Annual Research Plans to John Hancock contained Abbott's *nominal* spending numbers for each Program Compound, not Abbott's intended and reasonably *expected* spending numbers. In making my calculations, I have corrected for this inaccuracy by adjusting Abbott's nominal spending forecasts using a decision tree analysis that incorporates Abbott's own probabilities of success as described above.

76. Second, Mr. Hendricks' testimony also establishes that the historical spending reported by Abbott in its various Annual Research Plans and Program Status Reports to John Hancock was overstated in that it included Abbott's actual spending for the period from January 1, 2001 through the signing of the Agreement on March 13, 2001 (*i.e.*, the portion of 2001 that expressly was not included in the first Program Year). Abbott ultimately provided actual spending information for the first three months of 2001 to John Hancock, from which I was able to prepare corrected actual spending numbers

77. Using the decision tree analysis described above, I computed that in the Base Case, which utilized Abbott's own compound-specific success rates (Table 5), the 2003 expected Program Payment value was $33.6 million and the 2004 expected Program Payment value was $41.7 million. In the Low Case, utilizing CMR International's success rates (Table 6), the 2003 expected Program Payment value was $21 million and the 2004 expected Program Payment value was $36.8 million (See Table 21, below).

Table 21
But-for Program Spending
Expected Value of Program Payments
($ millions)

Item	Low Case	Base Case
Expected Value of Program Payments:		
2003 Program Payment	21.0	33.6
2004 Program Payment	36.8	41.7
Subtotal	**57.8**	**75.3**
Prejudgment Interest	**10.3**	**13.8**
Total	**68.1**	**89.1**

78. As I stated previously, the purpose of calculating these expected Program Payments was to consider an offset to damages resulting from an increase in spending by Abbott in the But-for Scenario in which there were actually nine viable Program Compounds instead of just six. If the three Misrepresented Compounds had been as viable as represented by Abbott at the time of the Agreement, and performed as reasonably expected in the But-for Scenario, then due to the increased program development life and increased Program Spending, Abbott likely would have forecast expected Program Spending in excess of $614 million in some circumstances. Therefore, it can be expected that John Hancock would have made one or both additional Program Payments. The expected value of those payments is approximately $58 million (Low Case) and approximately $75 million (Base Case), before prejudgment interest (*See* Table 21, above).

INDIVIDUAL DAMAGE SCENARIOS

79. For the convenience of the Court, I have also computed damages for each individual Misrepresented Compound. These calculations use the same models and methodologies outlined above. If the Court so instructs me, damage calculations reflecting different combinations of two Misrepresented Compounds can readily be provided using the same models and methodology outlined above. Table 22 displays a summary of my single compound calculations:

Table 22
Summary of Damage Calculations
Misrepresented Compound Variations
($ millions)

Misrepresented Compound	Scenario	Present Value of Lost Royalties	Present Value of Lost Milestones	Present Value of 2003 and 2004 Expected Program Payments	Net Total Prejudgment Interest	Total Damages*
ABT-518 Only	Low Case	5	0	0	0	**5**
	Base Case	26	(1)	0	0	**24**
ABT-594 Only	Low Case	41	3	0	1	**44**
	Base Case	131	(1)	0	2	**132**
ABT-773 Only	Low Case	181	14	0	6	**201**
	Base Case	271	11	(37)	2	**246**

Differences due to rounding

*Does not include damages related to the Spending Shortfall or Rescission calculations

SUMMARY

80. Table 23 summarizes my computations of the elements of John Hancock's damages encompassed by my testimony:

Table 23
Summary of John Hancock Damage Calculations*
($ millions)

Scenario	Present Value of Lost Royalties	Present Value of Lost Milestones	Spending Shortfall **	2003 and 2004 Expected But-for Program Payments	Total Damages
Low Case	225	19	31	(68)	**207**
Base Case	361	16	31	(89)	**319**

* Includes prejudgment interest
** *Alternative Abbott data suggests Spending Shortfall damages could alternatively be approximately $36 million*

81. In the event of rescission, I have computed that John Hancock would receive from Abbott $118 million, including prejudgment interest to December 31, 2007.

Signed under the pains and penalties of perjury this 28th day of January, 2008.

/s/ Alan Friedman
Alan Friedman

CERTIFICATE OF SERVICE

I hereby certify that this document is being filed with the Court through the ECF system and that a copy will be sent electronically to counsel for defendant through the ECF system on January 28, 2008.

/s/ Richard C. Abati
Richard C. Abati (BBO No. 651037)

PLs' ML

Portfolio Analysis of 2001 Abbott Global Pharmaceutical Development Assets

Addendum: Use of Productivity Index in Portfolio Selection

April 27, 2001

Key definitions - project value measures

- Expected Value (EV):
  - Risk adjusted Net Present Value (NPV) of a project
    - Incorporates base, upside and downside division margin projections.
    - Incorporates technical risk by phase.
    - NPV Division Margin calculated on years 2001-2015.
    - Discount rate = 12.5%
- Expected Commercial Value (ECV):
  - Probability-weighted average of base, upside and downside division margins.
- Productivity Index (PI):
  - Ratio of Expected Value to Expected R&D cost
  - "Bang for the Buck"

Phase Balanced Productivity prioritization balances short-term and long-term assets.

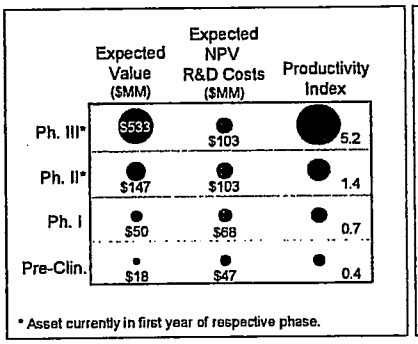
- **Expected Value**
  - Favors late stage development compounds.
  - Selects big development projects over smaller projects.
  - Doesn't ensure most productive use of R&D resources.
  - Not recommended to be used for portfolio prioritization.

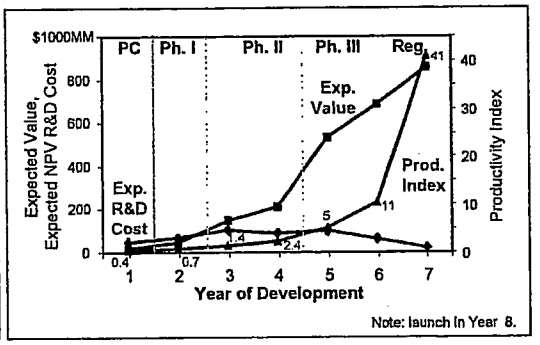
- **Productivity Index**
  - Ensures most productive use of R&D resources.
  - Strong bias towards Phase III &IV programs.
  - Late stage bias can result in phase mix imbalance.
  - Used only as productivity benchmark and not as primary portfolio optimization method.

- **Phase Balanced Productivity**
  - Ensures phase mix balance with high productivity.
  - Recommended methodology for portfolio selection, if feasible.

The R&D productivity index increases as an asset moves through development.

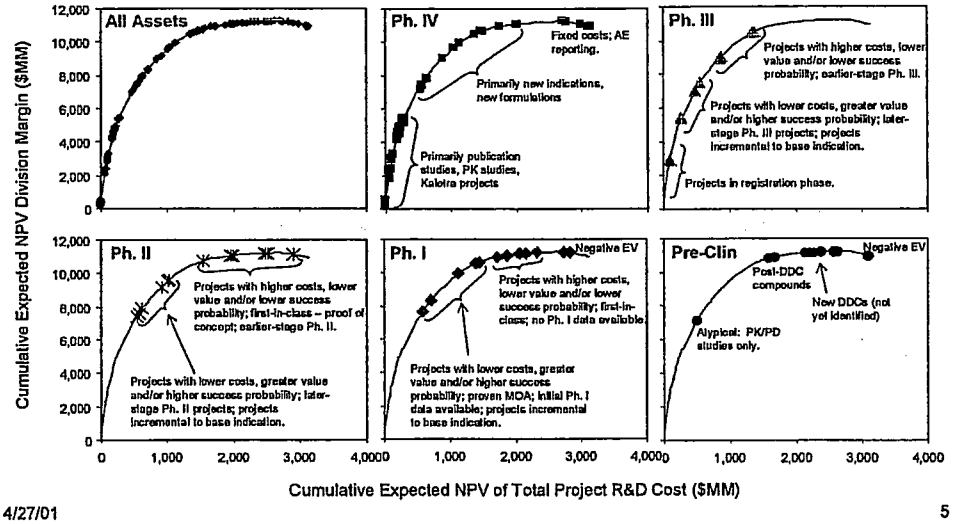
- Expected value increases (approaching realization of revenues and increasing probability of technical success).
- Expected costs rise modestly but ultimately decline (declining nominal costs offset by time value of money and probability of technical success).



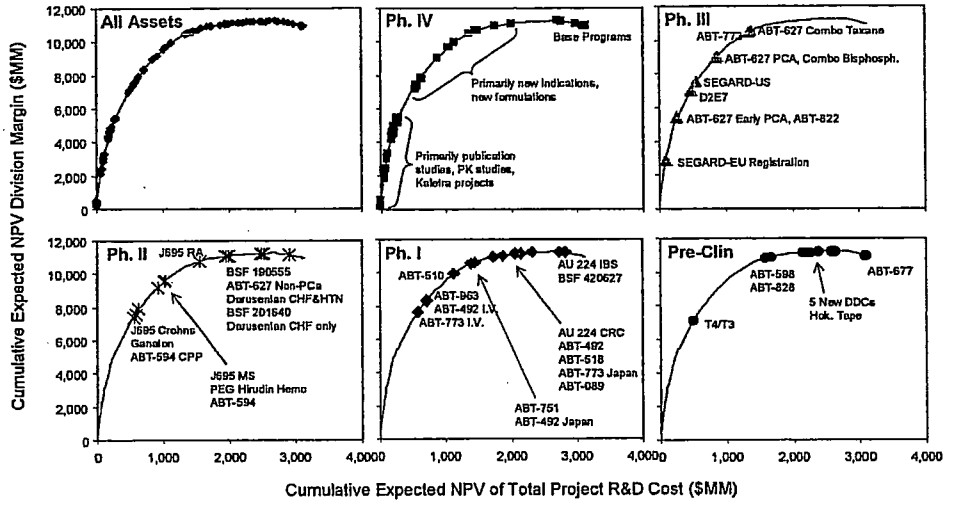


Note: Values are for an asset with $450MM peak year sales, which is currently in the respective year/phase of development. Abbott historical average development costs, timelines and technical success probabilities are assumed.

Projects on the steep part of the R&D productivity curve are generally in Ph. III or IV. Projects in Ph. II or earlier are found on the shallower part of the curve.



R&D productivity curve by phase – project detail.



PLs' MM

Risks in new drug development: Approval success rates for investigational drugs

Joseph A. DiMasi, PhD *Boston, Mass*

The drug development process is known to be complex, costly, and time-consuming.[1-3] The process is also risky in that most compounds that undergo clinical testing are abandoned without obtaining marketing approval. The rate at which pharmaceutical firms market new therapies in the United States is an important measure of the viability of the drug development process.[4] The cost of new drug development is also critically dependent on the proportion of drugs that fail in clinical testing.[5-7] Estimates of industry success rates can be used in benchmarking exercises for project planning purposes. Given the length and cost of the drug development process, careful consideration of all factors that have a significant impact on the process is needed to appropriately allocate research and development resources.

In a series of studies of new drug development in the United States, the Tufts Center for the Study of Drug Development (CSDD) and others have provided descriptive data on how cumulative success rates for new chemical entities (NCEs) vary with time from investigational new drug application (IND) filing.[1,8-14] Several studies have also examined clinical success rates for biotechnology-derived drugs.[15-17] Statistical modeling can be helpful in analyzing success rates for recent periods because many of the compounds will still be in active testing at the time of the analysis. Tufts CSDD has also conducted a number of studies that use this approach to predict final success rates for groups of compounds for which the ultimate fate of some of the compounds in the data set is not known.[4-7,18-20]

This study provides updated success rate analyses for NCEs. Success rate trends and variations in success rates by therapeutic class are presented. The hypothesis that pharmaceutical firms have been moving compounds through the process to either marketing approval or research abandonment more quickly is also examined. In addition, attrition rates for compounds entering clinical development phases are obtained. Finally, statistics on the reasons compounds fail in development are given.

METHODS

Data used for this study were obtained primarily from a Tufts CSDD database that contains information from ongoing surveys of pharmaceutical firms. The data provided for the most recent survey come from firms that have declined in number over the study period, as mergers have resulted in the combination of some of them. The data used for this study were obtained from the units and subsidiaries of what are now 24 parent firms. These firms provided data on NCEs first investigated in humans anywhere in the world or NCEs for which they were the first to file a US IND since 1963. The data gathered include IND filing dates, the dates on which IND research was abandoned, reasons for termination of research, the latest phase compounds were in when research was abandoned, and the date of new drug application approval. A description of additional information included in this database is available elsewhere.[1] Data were also obtained from public sources.[21,22] Current success rates for these NCEs were examined (as of December 31, 1999), and statistical analysis was applied to data on past rates of research abandonment and approval to predict future success rates. Analyses were conducted for NCEs with INDs first filed in 3- and 6-year periods from 1981 to 1992. Data on more recent INDs were available but, given the length of the NCE development

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0009-9236/2001/$35.00 + 0 13/1/115446
doi:10.1067/mcp.2001.115446

process, they are too recent to use for a comprehensive statistical analysis of success rates.

Inclusion criteria. For purposes of this study, an NCE is defined as a new molecular compound not previously tested in humans. Excluded are new salts and esters of existing compounds, surgical and diagnostic materials, vaccines and other biologic agents, certain externally used compounds (such as disinfectants, antiperspirants, and sunscreens), and nutritional compounds (such as natural forms of vitamins and sweetening agents). Our definition of an NCE differs from the FDA's definition of a new molecular entity. The most notable difference is that the FDA's definition includes diagnostics, whereas our definition of an NCE does not.

Statistical analysis of success rates. For the statistical analyses, residence time (the length of time from IND filing to either abandonment of research without marketing approval or to new drug application approval) was calculated for NCEs with INDs first filed in successive 3-year intervals from 1981 to 1992. Approval dates were available through December 31, 1999, and were used in determining observed success rates. Residence times were also calculated as of the end of 1999. Observed and predicted cumulative approval success rates were calculated at each year from IND filing.

NCEs were stratified according to source (self-originated versus licensed-in or otherwise acquired) and therapeutic class. An NCE is defined as self-originated if it was developed entirely under the auspices of the responding firm. We define acquired NCEs to be compounds that were obtained by the developing firm through licensing, purchase, barter, or other means. To determine whether trends in success rates exist, we analyzed the data by the period during which the IND was filed.

Predicted success rates for IND filing periods were determined from a 2-stage model of the approval process. NCEs with research still active as of December 31, 1999, constitute right-censored observations for our data set. Survival analysis can make use of information provided by censored data.[23] NCEs were assumed to survive until either research was terminated without approval or marketing approval was achieved. Details of the selected models and the computational approach used to estimate final success rates are provided in the Appendix.

The survey data also provided information on the latest development or regulatory phase that abandoned NCEs were in at the time of termination. These data allow us to determine the distribution of research terminations by phase. In combination with predicted approval rates for IND filing intervals, they also permit us to estimate the probability of approval once a compound enters a given clinical phase and phase attrition rates (the percentage of compounds that enter a phase that are abandoned before the next phase is initiated).

RESULTS

Included in the CSDD database of investigational compounds are the development histories of 671 NCEs for which survey firms had filed a first IND from 1981 to 1992. Of these, 508 were identified as self-originated and 163 were identified as acquired. Of the 508 self-originated NCEs, 350 were initially investigated in humans in the United States. By the end of 1999, 20.9% of the NCEs with INDs filed from 1981 to 1992 had been approved for marketing in the United States. For this period, the current US approval success rates for NCEs that were acquired, self-originated, and self-originated and first tested in humans in the United States are 33.1%, 16.9%, and 8.6%, respectively. These results illustrate the significance of previous testing on measured US success rates; success rates on IND filings are higher for compounds that were licensed-in or first tested abroad.

Time to research termination. Even though some of the drugs in our database are still active, survival analysis can be used to establish the rates at which the NCEs with INDs filed during a given period will be dropped from active testing. The mean and median times to research termination for self-originated NCEs that were abandoned with INDs first filed during the periods from 1981 to 1983, 1984 to 1986, 1987 to 1989, and 1990 to 1992 are shown in Fig 1. Because NCEs in the later intervals had less time for research to be terminated, the averages for the later periods may be somewhat understated relative to the earlier periods. However, previous research and our current data suggest that the likelihood of approval, as opposed to abandonment, increases with time from IND filing. If we could add termination times for NCEs that will eventually be terminated, the impact should be much less on the median than on the mean.

Even with these qualifications, the results at least suggest that, over time, pharmaceutical firms have made quicker decisions on research failures. Mean residence time decreased 30% (1.5 years) from the 1981–1983 to the 1990–1992 IND filing intervals. Median time to research abandonment decreased 20% (0.8 years) for INDs filed in the early 1990s relative to the early 1980s.

Further evidence that the ultimate fate of investigational NCEs has tended to be resolved more rapidly

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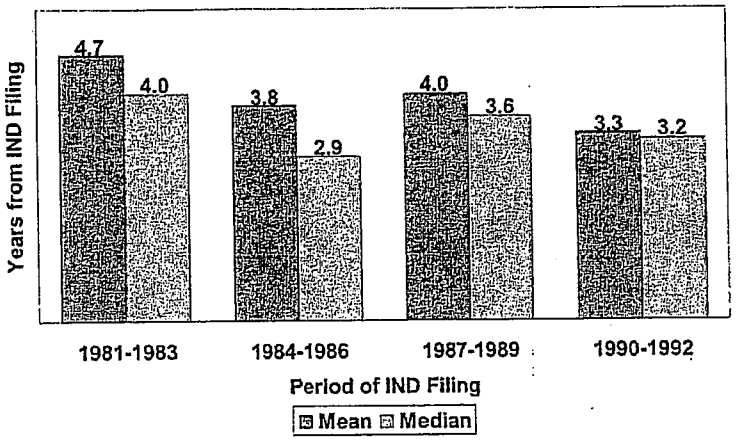

Fig 1. Mean and median time to research abandonment for self-originated new chemical entities (NCEs) with a first investigational new drug application (IND) filed during a given period.

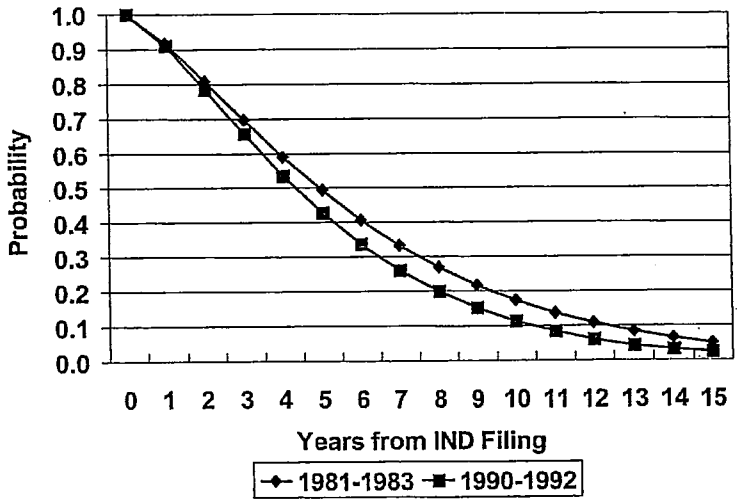

Fig 2. Estimated survival curves for self-originated NCEs with a first IND filed during a given period. The curves show the percentage of NCEs that had not been abandoned or approved for marketing in the United States (ie, still active) a given number of years from the date of IND filing. The data were fitted to Weibull distributions.

over time is shown in Fig 2. The *curves* in the figure are estimated survival curves for the 1981–1983 to 1990–1992 IND filing intervals. A *point* on the curve represents the probability that an investigational NCE will still be active a given number of years from IND filing. An NCE is inactive at a given point in time if either research has been abandoned without marketing approval or the compound has received FDA approval for marketing. It should be noted that the estimated survival curves account for censored data; that is, information regarding still active NCEs is used to estimate final survival rates.

Median survival time decreased from 4.9 years to 4.3 years (12%) for the 1981–1983 to 1990–1992 filing intervals, respectively. Faster action is also evident in the figure for different amounts of time from IND filing. The percentages of NCEs for the 1990–1992 filing period that are still active are 6 to 7 percentage points lower than those for the 1981–1983 filing period at 4 to 10 years from IND filing.

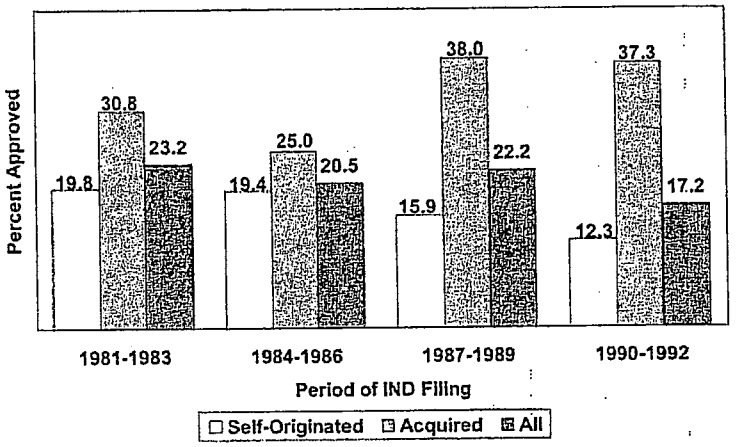

Fig 3. Current clinical approval success rates for NCEs by origin and period during which a first IND was filed.

Success rate trends. To estimate final success rates, results from the survival analyses must be combined with those from qualitative choice models of the conditional probability of approval at given residence times. The parameter estimates for both stages of the model are highly statistically significant, and goodness-of-fit measures indicate strong agreement with the data. The parameter estimates used to determine the predicted final success rates reported here and the accompanying statistical results are available upon request.

Current success rates (as of December 31, 1999) for self-originated, acquired, and all NCEs by IND filing interval are shown in Fig 3. Licensed compounds generally have undergone some testing before licensing and have been shown to be promising candidates for marketing approval. The results support the hypothesis of such a screening effect for acquired NCEs; current success rates for acquired NCEs are notably higher than those for self-originated NCEs.

A screening effect also appears to apply to self-originated compounds that have undergone some clinical testing abroad before an IND has been filed in the United States. The success rates for self-originated NCEs that were first tested in humans in the United States are much lower than the success rates for all self-originated NCEs. Current success rates by IND filing interval for self-originated NCEs first tested in the United States are 33% to 65% lower than for self-originated NCEs as a whole.

Censoring has an impact on the results for all IND filing intervals, but the effect is much greater for the more recent intervals. The proportions of NCEs that are currently active are substantially higher for these later periods. Thus the lower current success rates for self-originated NCEs in the 1987–1989 and 1990–1992 intervals may simply reflect the shorter amount of time available for the ultimate fate of those NCEs to have occurred. Trend analysis for these later periods must be aided by the application of statistical techniques to forecast approval rates for the active NCEs.

Current success rates, maximum possible success rates (assuming all active NCEs are approved), and predicted final success rates for self-originated NCEs by IND filing interval are shown in Fig 4. The predicted final success rates fall between current and maximum possible success rates for all filing intervals. Although both predicted and maximum possible success rates are lower for the 1987–1989 interval relative to the intervals in the earlier 1980s, the predicted success rate for the 1990–1992 interval is 16% higher than for the interval with the next highest predicted success rate.

Comparison of predicted and actual success rates for the early time periods can validate the performance of the statistical model. For NCEs with INDs first filed from 1981 to 1983, the model predicts a cumulative success rate of 19.5% at 16 years from IND filing (the maximum amount of time available for all compounds in the group); the actual success rate for this group at 16 years from IND filing is 19.8%. Similarly, NCEs with INDs first filed from 1984 to 1986 have a predicted success rate of 18.8% at 13 years from IND filing and an actual success rate of 19.4%.

Therapeutic classes. Previous research has indicated that success rates for NCEs vary by therapeutic

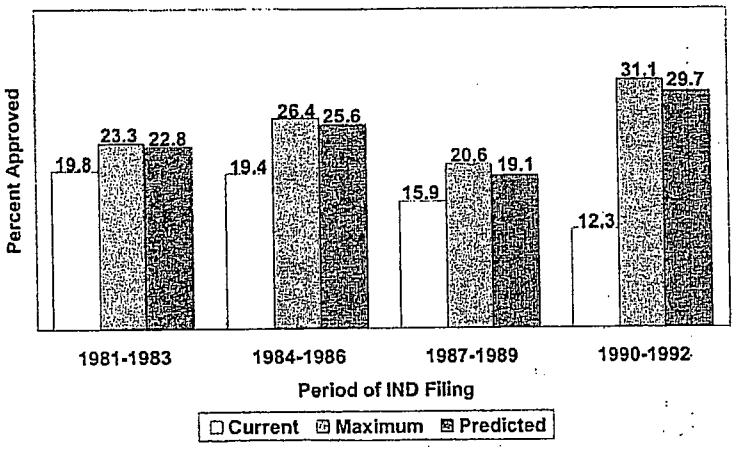

Fig 4. Current (as of December 31, 1999), maximum possible, and predicted final clinical approval success rates for self-originated NCEs by period during which a first IND was filed. Maximum possible success rates were determined under the assumption that all active compounds are eventually approved for marketing. Predicted success rates were constructed with use of estimates for a survival analysis of residence time (time from IND filing to abandonment or US marketing approval) with a Weibull distribution specification and estimates for the conditional probability of approval for a given residence time with a probit specification.

Table I. Current and maximum possible success rates by therapeutic class for self-originated NCEs with INDs first filed from 1981 to 1992*

Therapeutic class	*NCEs*	*Approved NCEs*	*Open NCEs†*	*Current success rate†*	*Maximum success rate‡*
Analgesic/anesthetic	49	10	4	20.4%	28.6%
Anti-infective	57	16	3	28.1%	33.3%
Antineoplastic	38	6	6	15.8%	31.6%
Cardiovascular	120	21	6	17.5%	22.5%
Central nervous system	110	16	14	14.5%	27.3%
Endocrine	33	6	4	18.2%	30.3%
Gastrointestinal	15	3	2	20.0%	33.3%
Immunologic	13	2	0	15.4%	15.4%
Respiratory	25	3	0	12.0%	12.0%
Miscellaneous	43	3	4	7.0%	16.3%

NCE, New chemical entity.
*Therapeutic class information is missing for five compounds.
†As of December 31, 1999.
‡Assumes that all open NCEs will eventually be approved.

class.[6,20] The current and maximum possible success rates by IND filing interval for self-originated NCEs in 9 specific therapeutic categories are shown in Table I. Because the number of compounds available for analysis is greatly reduced when the data are stratified into therapeutic categories, the entire study period (1981–1992) is used. For the immunologic and respiratory categories the fate of all of the NCEs is known so that current, maximum, and final success rates are the same.

For many of these therapeutic classes, the number of compounds with IND filings in an interval is too small for accurate statistical estimation. However, we had enough data and the fits with the statistical model described above were sufficiently good for us to estimate predicted final success rates for the analgesic/anesthetic, anti-infective, cardiovascular, and central nervous system categories. The current, maximum possible, and predicted final success rates for these 4 classes are shown in Fig 5. Relative success rate results for these

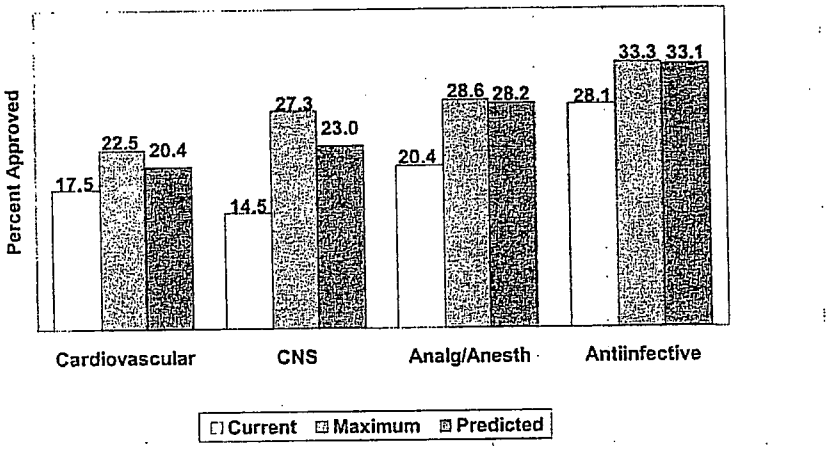

Fig 5. Current (as of December 31, 1999), maximum possible, and predicted final clinical approval success rates by therapeutic class for self-originated NCEs with a first IND filed from 1981 to 1992. Maximum possible success rates were determined under the assumption that all active compounds are eventually approved for marketing. Predicted success rates were constructed with use of estimates for a survival analysis of residence time (time from IND filing to abandonment or US marketing approval) with a Weibull distribution specification and estimates for the conditional probability of approval for a given residence time with a probit specification.

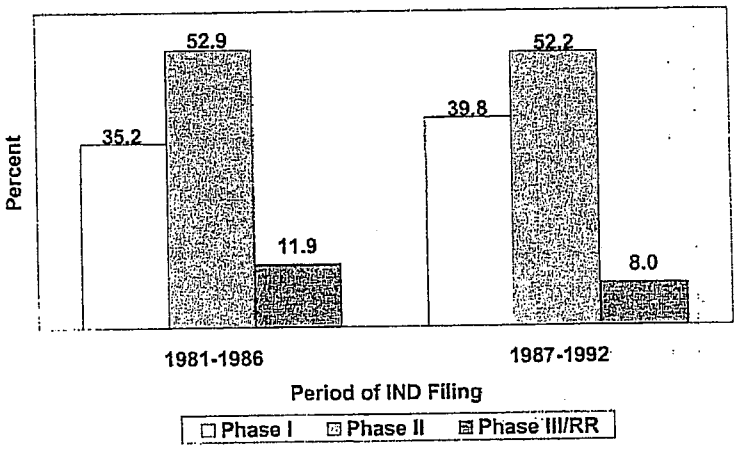

Fig 6. Distribution of research terminations for self-originated NCEs by clinical phase and period during which a first IND was filed.

classes are likely unaffected by time trends inasmuch as the number of filings for the last half of the study period as a percentage of total filings for the whole period for each of these 4 classes varied only from 47% to 55%. The predicted success rates range from approximately 1 in 5 for cardiovascular NCEs to 1 in 3 for anti-infectives.

Clinical phase attrition rates. Clinical approval success rates yield patterns of success for the clinical development process as a whole, but they do not inform us of success and failure patterns during the clinical development process. Our data on the latest phase that an abandoned NCE was in at the time of termination give us a distribution of research terminations by phase. The distribution for self-originated NCEs is shown in Fig 6. Approximately half of clinical research failures occur in phase II. This is the case for both the first and second halves of the study period. For the later IND fil-

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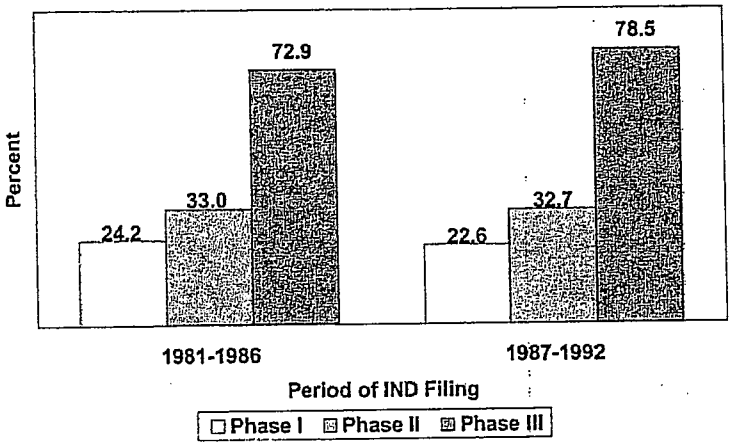

Fig 7. Approval success rates for self-originated NCEs entering a given clinical phase.

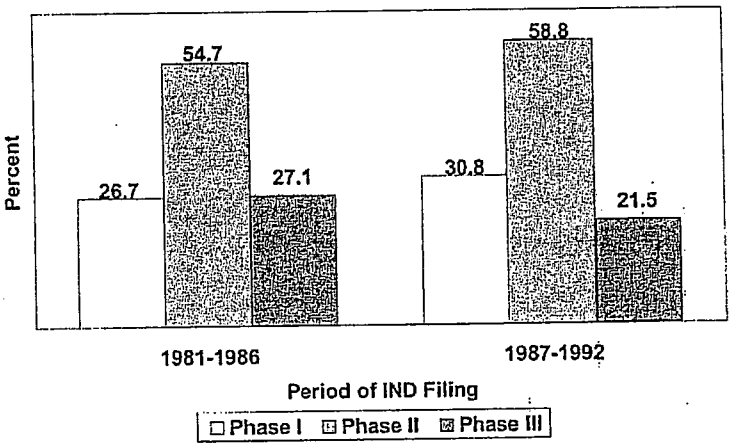

Fig 8. Phase attrition rates (percentage of compounds entering a phase that fail in the phase) for self-originated NCEs by period during which a first IND was filed.

ing period, however, proportionately more research failures occurred in phase I and proportionately fewer occurred in phase III or regulatory review.

Statistical analysis yields predicted final success rates for self-originated NCEs for the 1981–1986 and 1987–1992 filing intervals of 24.2% and 22.6%, respectively. Current approval and termination rates for these periods, along with the assumption that currently active NCEs that are predicted to eventually fail will do so in phase III or regulatory review, allow us to predict approval rates for NCEs that enter a clinical phase (Fig 7). Although approval rates are similar for the early clinical phases in both periods, the likelihood of approval increased by 5.6 percentage points for phase III. This is consistent with the results displayed in Fig 6, which showed relatively more terminations in phase I and relatively fewer in phase III or later.

The data on research terminations by phase and predicted success rates also allow us to determine phase attrition rates. Fig 8 shows that attrition rates are greatest in phase II in which more than half of the investigated compounds fail. During the study period, failure rates increased for phases I and II but declined for phase III.

Reasons for research abandonment. The database contained information on the reasons research was abandoned for NCEs that had research terminated without marketing approval. We grouped the responses into 3 major categories: safety (eg, "human toxicity" or "ani-

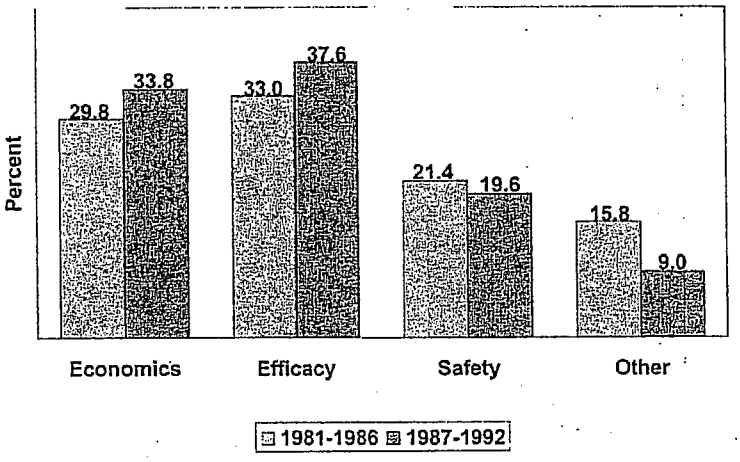

Fig 9. Percentage of research terminations for all NCEs by period of first IND filing and by primary reason for abandonment.

mal toxicity"), efficacy (eg, "activity too weak" or "lack of efficacy"), and economics (eg, "commercial market too limited" or "insufficient return on investment"). A relatively small number of the compounds that had been abandoned had reasons for termination that were not specific enough to be placed in 1 of these 3 categories. The shares of all reasons for abandonment for each of these categories by IND filing interval are shown in Fig 9.

For the last half of the study period, economic and efficacy issues became relatively more prevalent, while safety issues became relatively less prevalent, as reasons for research termination. Because the time available for the fate of the compounds to have been determined is limited, the abandonment results for the interval from 1987 to 1992 are biased toward causes that tend to be revealed relatively soon after filing. This censoring effect also applies to the earlier interval but with much less impact. The economic share increased, even though research on NCEs terminated for economic reasons tends to occur later in the development process than is the case for safety and efficacy (eg, for filings from 1981 to 1986, 45% of the economic terminations occurred at least 6 years from filing compared with 35% of efficacy and 17% of safety terminations).

The censoring effect also applies when the data are analyzed by the phase that a compound was in when it was abandoned. This bias will tend to be lower if earlier periods are examined. Considering the first half of the study period (NCEs that had an IND first filed from 1981 to 1986), compounds that had failed for economic or efficacy reasons were terminated much more frequently in late clinical testing phases. The percentage of failed compounds that were abandoned in phase III or during the regulatory review period was 26.6% for economic failures, 24.0% for efficacy failures, and 8.3% for safety failures.

Table II shows mean and median abandonment times for all NCEs by IND filing period and by the primary reason for termination. Average times to abandonment are lower for the later filing period, but this can result in part from the shorter period during which abandonments can occur for this interval. For either period, however, both the mean and median time to research abandonment is longer for NCEs that were terminated primarily for economic than for other reasons. The data also show that economic considerations were the most frequent determinants underlying decisions to terminate late-stage clinical research. During the entire study period, 39% of the terminations that occurred at least 4 years from filing were for economic reasons, 32% were related to efficacy issues, and only 16% were for safety problems (13% were for other reasons).

DISCUSSION

A statistical model of the rate at which new drugs proceed through clinical testing to marketing approval was estimated for three 4-year and two 6-year IND filing intervals. Estimated approval success rates for self-originated NCEs varied from 19% to 30% during the study period. The highest predicted success rate was for the most recent filing period (1990–1992). The results suggest that approval rates have not declined over time and, quite possibly, have increased. A general improvement in success rates can result from bet-

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Table II. Time to research abandonment (in years) for NCEs by IND filing period

	1981-1986			*1987-1992*		
Reason	*n*	*Mean (y)*	*Median (y)*	*n*	*Mean (y)*	*Median (y)*
Economics	64	4.4	4.0	45	3.7	3.2
Efficacy	71	3.6	2.3	50	2.7	2.6
Safety	46	2.6	2.5	26	2.1	1.2
Other	34	3.5	2.3	12	2.7	2.2

IND, Investigational new drug application.

ter preclinical screening. The implications for the development process are significant because the clinical costs for some research failures will not be borne if success rates increase. However, these savings would have to be balanced against any additional costs associated with a better preclinical screening process.

Success rates for self-originated NCEs differed significantly by therapeutic class. Predicted or actual final success rates varied from 12% for respiratory drugs to 33% for anti-infectives. Cardiovascular and central nervous system drugs also had predicted success rates that were substantially below that for anti-infectives. Some of the differences in success rates by therapeutic class might be explained generally by differences in the uncertainty with which regulatory standards would be satisfied. For example, efficacy end points for anti-infectives are usually clearly defined and relatively easy to assess. In contrast, the difficulties in establishing efficacy for psychotropic compounds have been well described.[24,25]

The length of time that an NCE spent in clinical testing or regulatory review before the fate of the drug (abandonment or approval) was determined decreased during the study period. Estimated median survival times for self-originated NCEs decreased 0.6 years for IND filings in the early 1990s compared with those a decade earlier. These results are consistent with data on shorter US clinical development times for late 1990s approvals.[2,3] In addition, our data on the time to research termination for compounds that have been abandoned suggest that pharmaceutical firms have been abandoning unsuccessful compounds more quickly. Faster failures and shorter development times for drugs that do get approved imply, other things being equal, lower research and development costs per approved new drug. However, these gains can easily be offset if the out-of-pocket costs of conducting clinical trials have increased.

Our data on clinical phase attrition rates not only support the hypothesis that pharmaceutical firms have acted more quickly in terminating development on unsuccessful compounds but also allow us to better pinpoint when in the process these gains were made. Development costs are reduced more if a compound that ultimately fails is abandoned sooner. Our results indicate that firms have indeed tended to abandon their failed compounds earlier in the process. Reductions in failure rates for phase III and regulatory review appear to be associated with corresponding increases in failure rates for phase I. It should be noted, however, that quicker decisions to abandon projects may also increase the likelihood of making a type II error (accepting the hypothesis that an investigational drug will not meet efficacy and safety standards and earn a reasonable return when in fact it would have done so if pursued). Furthermore, failure rates for phase II testing remained essentially constant. Some expensive phase III trials may be avoided if phase II testing can be made more informative so as to weed out more of those compounds that will fail to achieve regulatory approval.

Our results indicate that commercial factors became relatively more important over time as the primary reason for abandoning development of investigational NCEs. Censoring may affect the results for the more recent time periods. NCEs that failed for economic reasons, however, tended to last longer in testing than NCEs that failed for efficacy or safety reasons. Thus the censoring in the data suggests that the final results will show that the trend for economics is even steeper than currently observed. Given that economic factors increased in importance as a reason for research termination and that these commercial considerations have tended to be a deciding factor relatively late in the development process, the improvement in attrition rates that we have observed is all the more impressive.

Clinical success rates and phase attrition rates for new drugs are important indicators of how effectively pharmaceutical firms are using the resources that they devote to research and development. The proficiency with which this is done is a consequence of a complex set of regulatory, economic, and firm-specific factors. Reliable success rate and phase attrition rate estimates are an important tool for evaluation of the efficiency with which industry conducts clinical drug development. Our results on the risks in drug development should aid in this process.

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APPENDIX

Success rates are predicted by combining 2 separate statistical estimation procedures. Specifically, the cumulative probability of approval at t years from IND filing is given by the following:

$$S(t) = \int_0^t f(u) \cdot P(u) \cdot du \qquad (1)$$

in which f(u) is the probability density function for the survival-time data, P(u) is the probability of approval given a residence time of u.

The density function, f(u), can be estimated by a parametric survival analysis. Various theoretical distributions (ie, exponential, Weibull, log-normal, and log-logistic) were fitted to the survival-time data. Estimated survival and hazard rate curves derived from nonparametric techniques, such as life-table analysis or the Kaplan-Meier technique, can be used as a first step in determining whether the data are consistent with these parametric forms. Likelihood ratio tests based on the log-likelihood values obtained from fitting particular parametric forms to the data can also be used to test whether one distribution fits the data better than another. The estimated survival and hazard rate curves from life-table analyses and the likelihood ratio tests suggested that Weibull distributions best fit the data.

Specification of the Weibull distribution (a generalization of the exponential distribution) requires esti-

mates of two parameters. In particular, the probability density function for the Weibull distribution is given as follows:

$$f(u) = \gamma \cdot \alpha \cdot u^{\gamma-1} \cdot e^{-\alpha \cdot u^{\gamma}} \qquad (2)$$

$$u \geq 0 \quad \alpha,\gamma > 0,$$

where u is residence time. For this distribution, statistical software gives estimates of μ and σ where $\gamma = 1/\sigma$ and $\alpha = e^{-\mu/\sigma}$. The values obtained are maximum likelihood estimates in which a Newton-Raphson algorithm is used to solve the first-order conditions.

NCEs with a given residence time have terminated with either research abandonment or marketing approval. Because the possible responses are qualitative and binary, qualitative choice modeling is an appropriate and feasible method for estimating P(u). Parametric forms that have proved useful in many applications of this type are the probit and logit specifications. We examined both of these specifications. The parameters were estimated by a maximum likelihood technique in which a modified Newton-Raphson algorithm was used to solve the first-order conditions. Log-likelihood values for the estimations can be used to discriminate among the models. The log-likelihood values suggested the probit form for P(u). In general, however, the results were not sensitive to the choice of model.

In the context of this application, the probit model posits that the cumulative probability of approval varies with residence time according to the cumulative standard normal distribution evaluated at a linear function of residence time. In particular, we estimated the parameters, α and β, of the following function:

$$P(\alpha + \beta \cdot u) = \int_{-\infty}^{\alpha+\beta \cdot u} (1/\sqrt{2 \cdot \pi}) \cdot e^{-z^2/2} \cdot dz, \qquad (3)$$

where u is residence time. This specification has the property that the conditional probability of approval increases (in a sigmoidal fashion) with the time from IND filing.

Once parameter estimates are obtained, equations 2 and 3 can be substituted into equation 1 to determine a success rate at a given number of years from IND filing. We are also interested, though, in final success rates for NCEs with INDs filed during a given interval. Both the Weibull density function and the conditional probability of approval determined from the probit specification vary with time and, in theory, no ceiling can be placed on the time from IND filing. Thus the two-stage model predicts as a final success rate (S_F) the following limit:

$$S_F = \lim_{t \to \infty} S(t) \qquad (4)$$

assuming that the limit exists. Unfortunately, we do not have a closed-form solution for equation 1. However, if the limit does exist, we can then use numerical techniques to adequately approximate S_F with S(T) for large enough T. In choosing T, we adopted two criteria. First, T must be large enough so that the probability density function (2) integrated up to T is within one-half of 1% of one. Second, the estimated cumulative probability of success [S(t)] must have stopped increasing out to 3 places after the decimal point. Thus our approximation of S_F should be accurate to within one-tenth of 1%. For all of the predicted success rate estimates given here, T = 30 years easily meets the two criteria. Therefore all of the survival and predicted cumulative success rate curves presented here are shown out to 30 years from IND filing.

PLs' ND

RETURNS ON R&D FOR

1990s NEW DRUG INTRODUCTIONS

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March, 2002

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ABSTRACT

Previously published research by two of the authors found that returns on R&D for drugs introduced into the market in the 1970s and 1980s were highly skewed and that the top decile of new drugs accounted for close to half the overall market value. In the 1990s, there have been significant changes to the R&D environment for new medicines: the rapid growth of managed care organizations; indications that R&D costs are rising at a rate faster than overall inflation; new market strategies of major pharma firms; increased alliances with the emerging biotech sector; and, the increased attention focused on the pharmaceutical industry in the political arena. Nevertheless, analysis of new drugs entering the market from 1990-1994 resulted in findings similar to the earlier research—pharmaceutical R&D is characterized by a highly skewed distribution of returns and a mean industry internal rate of return modestly in excess of the cost-of-capital. These findings provide support for a model of intensive R&D competition by pharmaceutical firms to gain economic advantage through product innovation and differentiation.

I. INTRODUCTION

Competition in the research based pharmaceutical industry centers around the introduction of new drug therapies. In this paper, we examine the returns on R&D for new drug entities introduced into the U.S. market in the first half of the 1990s. This research work builds directly on earlier analyses of

returns on R&D for the 1970s and 1980s introductions performed by Grabowski and Vernon[1, 2].

Our prior analyses indicate that this industry has exhibited very skewed distributions of returns. In this regard, several significant new classes of drug therapies have been introduced since the late 1970s. Early movers in these classes have obtained the highest returns on R&D. We found that the top decile of new drugs accounted for close to half of the overall market value associated with all the new drug introductions in our 1970s and 1980s samples.

The results of our prior analysis are also consistent with an economic model of rivalrous R&D competition. In particular, the promise of above average expected returns produces rapid increases in industry R&D expenditures, as firms compete to exploit these opportunities, until returns become unattractive. From an industry perspective, our results indicate that mean returns on R&D are relatively close in value to the risk adjusted cost-of-capital for drug industry investments. This rent-seeking model is also supported by a recent empirical analysis by Scherer, who finds a strong relationship between industry R&D outlays and profits over the period of 1962 to 1996[3].

An investigation into the drug returns in the 1990s is timely on a number of grounds. First, this decade has been characterized by the rapid growth of managed care organizations on the demand side of the market for pharmaceuticals[4]. This has led to greater access to and utilization of pharmaceuticals, but also greater generic competition in the post-patent period. Second, a new study of R&D costs by DiMasi, et al. indicates that the R&D costs for new drugs have continued to rise much faster than the rate of general inflation.[5] This reflects, among other factors, the increased size of clinical trials compared to those for earlier new drug introductions. Third, many firms are changing their market strategies and attempting to launch their products simultaneously across world markets, reflecting the higher R&D investment costs and more intensive competition from new molecules in the same product class.

In addition to these economic developments, the industry continues to be the subject of considerable attention by policy makers. Recent policy initiatives include a Medicare prescription drug benefit, the parallel importation of drugs from Canada and Mexico, and various state programs affecting drug costs and utilization of the poor and elderly populations. The potential effects of these policy initiatives on R&D returns remain an important issue for research. Our past work on R&D returns has provided a framework for the Congressional Budget Office and other groups to consider the effects on R&D of the proposed Clinton Health Care Reform Act and the Waxman-Hatch Act of 1984[6, 7].

The plan of the paper is the following. In the next section, we describe the data samples and methodology for our analysis of the returns to 1990-94 new molecular entities (NMEs). Section III presents the empirical findings on the distribution of returns and a sensitivity analysis involving the main economic parameters. Section IV provides a discussion of the results and comparisons with the historical findings from our prior work which is based on the same methodology. The final section provides a brief summary and conclusion.

II. METHODOLOGY AND DATA INPUTS

A. Overview

This section explains the methodology and key data inputs used in estimating the returns to 1990-94 new chemical entities (NCEs)..(1) A detailed discussion of the general methodology is provided in our earlier papers on R&D return[1, 2]. Our focus here is on the similarities and differences of the 1990s sample from our analysis of prior NCE cohorts.

The basic sample is 118 NCEs introduced into the United States between 1990 and 1994. This is a comprehensive sample of the NCEs originating from and developed by the pharmaceutical industry that were introduced into the United States in the 1990-94 time period.(2) The number of NCE introductions has increased significantly in the early 1990s compared to the 1980s. The corresponding 1980-84 NCE sample was 64 NCEs. This increase in NCEs reflects the increased R&D expenditures for new entities by the traditional pharmaceutical industry as well as the growth of the independent biopharmaceutical industry.[8] The latter industry was in its infancy in the early 1980s, but by the early 1990s it had become a significant source of new drug introductions.(3)

Our basic procedure is as follows: for each new drug in our sample, worldwide sales profiles are constructed over the drug's complete product life cycle. These sales values are converted to after-tax profits and cash flow values using industry data on profit margins and other economic parameters. These data are combined with R&D investment information, based on the recent analysis by DiMasi et al.[5] Mean NPVs and IRRs are then computed for this portfolio of new drug introductions. The distribution of returns is another major focus of our analysis.

B. Cost-of-Capital

In our earlier analysis of 1980 NCEs, we utilized a 10.5% real cost-of-capital for the pharmaceutical firms. This was based on an analysis of the industry using the capital asset pricing model (CAPM) that was performed by Myers and Shyum-Sunder.[9] Their study was commissioned by the Office of Technology Assessment as part of a larger study on R&D costs, risk and rewards.[10] They found that the real after-tax cost-of-capital on equity plus debt varied between 10% and 11% during the 1980s.

For our sample of 1990-94 introductions, the relevant investment period spans the mid-1980s through the late 1990s. In their original article, Myers and Shyum-Sunder provided estimates of the cost-of-capital for 1985 and 1990. Myers and Howe have subsequently provided a related analysis for 1994.[11] We also performed a comparable CAPM for analysis for January 2000. The results of these CAPM based studies are summarized in DiMasi et al.[5]

Using these four CAPM based analyses, occurring at roughly five year intervals, we found that the mean cost-of-capital for pharmaceuticals over this period was just over 11%. Consequently, 11% was selected as the baseline value for the cost-of-capital in this analysis of 1990 NCEs. This represents a small increase from the 10.5% cost-of-capital utilized for the 1980 NCEs.

As Myers and Shyum-Sunder indicated in their original article, the CAPM approach provides somewhat conservative cost-of-capital values with respect to investment in new prescription drugs. One reason is the equity market data on which the CAPM analysis is based pertains to all the different functional areas and commercial activities of drug firms (which can include over the counter drugs, animal health, basic chemicals, etc.). Another reason that the cost-of-capital may be understated is the fact that many pharmaceutical firms carry significant cash balances.(4)

One of the authors undertook an informal survey of six pharmaceutical firms in mid-2001 with respect to the hurdle rates that drug firms utilize in their R&D investment decisions. The survey of these firms yielded (nominal) hurdle

rates from 13.5% to over 20%. If one takes 3% as the long-run expected rate of inflation, then an 11% real rate-of-return, corresponds to a nominal rate of 14%. This 14% rate is within the range of hurdle rates utilized by the drug firms in their R&D investment decisions, but it is at the lower end of the range. This is consistent with the view that a CAPM analyses provides conservative estimates on the industry's cost-of-capital.[6]

C. R&D Investment Expenditures

To obtain representative R&D investment expenditures for the new drug entities in our sample, we rely on the recently completed study by Di Masi et al.[5] This study obtained R&D cost data for a randomly constructed sample of 68 drugs that were first tested clinically between 1983 and 1994. The DiMasi study is designed to measure the average cost of a new drug introduction and includes discovery costs as well as the costs associated with failed candidates.

The mean introduction of our sample NCEs is 1992 while the mean introduction of drug candidates analyzed in the DiMasi study is 1997. DiMasi and colleagues had previously undertaken an analysis of the costs of 1980s introductions using the same methodology employed in their new study.[13] That study was centered around 1984. Given the availability of these two R&D cost studies centered around 1984 and 1997, we can utilize a linear extrapolation procedure to estimate the mean R&D costs for our sample cohort.[7]

Using this extrapolation procedure, we estimated the mean out-of-pocket R&D expenditures for the drugs in our sample to be $308.4 million. This is approximately double the estimated R&D expenditures (in 2000 dollars) for the 1980-84 samples of NCEs. DiMasi also estimated a representative investment period of 12 years from initial drug synthesis to FDA approval. We were able to allocate the out-of-pocket R&D costs over this 12 year period using weights derived from the DiMasi study. Capitalizing these costs to the date of marketing, at a real cost-of-capital of 11%, yields $613 million as the average (pre-tax) capitalized R&D investment per '90-'94 NCE introduction.

Our analysis is performed on an after-tax basis. For the time period under study, we estimate a 30% average effective tax rate for the pharmaceutical industry (see Section II-G). Since R&D expenditures can be expensed for tax purposes, we multiplied the pre-tax values by 0.7 to get an after-tax value. This is shown in the first row of Table 1. Utilizing the 30% effective tax rate, 613 million pre-tax capitalized corresponds to an after-tax value of $429 million.

In addition to these pre-launch R&D expenditures, firms also undertake R&D outlays in the post approval period for product extensions such as new indications, formulations and dosage levels. Since these activities can be viewed as spillovers from the original NCE introduction, these ongoing R&D investment expenditures, as well as any extra revenues that they generate, are appropriately incorporated into the analysis. Based on the DiMasi et al study, we estimated the average post-approval R&D costs per NCE in our sample period to be $107 million (before tax).[8] We allocated these costs equally over the first eight years of a NCEs market life, using a discount rate of 11% from the date of marketing. This yields a present value of $73 million (before-tax) and $51 million dollars (after-tax).

Adding the after-tax values (Col. 2 of Table 1), the mean capitalized value for both pre and post approval R&D for the drugs in our sample is estimated to be $480 million. This is the baseline value that we compare to the present value of net revenues for the mean NCE in our sample.

D. Global Sales

In our prior analysis, we obtained U.S. sales data on each NCE in the sample. We then estimated worldwide sales for these compounds using a worldwide sales multiplier that was common to all NCEs. One limitation of this approach is that the ratio of worldwide sales to domestic sales varies significantly, both over time and across drugs in our sample.

In the current analysis, our approach was to obtain worldwide sales data directly on as large a group of the drugs as possible. We were generally

successful in this endeavor, in the sense that we were able to obtain worldwide sales data for a majority of the NCEs in our sample (66 NCEs) using several complementary data sources. These 66 drugs accounted for over 90% of total U.S. sales realized by our sample of NCEs and presumably a similar, or even larger share, of their realized worldwide sales. With respect to the latter point, there is evidence that the larger selling U.S. drugs diffuse across more countries and have larger sales globally than U.S. compounds with smaller domestic sales.[14]

To obtain worldwide sales data, we collected sales data that firms provide in their annual reports, in the reports of financial analysts, and in publications such as Med Ad News. The latter source has compiled an annual survey of worldwide drug sales, by product, since 1990 on an expanding basis over time. The compilation for 2000 includes information on the top 500 selling prescription drugs worldwide.[15]

A complementary source of data that we also relied on is IMS data on worldwide sales, which is based on audit data sources from a large number of countries. The IMS data source was available to us (from a prior project) for a sub-sample of drugs consisting of the very largest selling global drugs in our sample. It provided a check on the sales information provided by the company sources. In most cases, the IMS sales values were less than the company figures. This reflected the fact that IMS does not capture all the sales channels available across countries, while the company data does include every channel.

In about 25% of the overlapping observations, however, the IMS sales were greater than the company reported values. An analysis into why this was the case revealed that the sub-sample of drugs with higher IMS sales was marketed internationally under multiple names and by several different companies. Consequently, sources such as Med Ad News didn't capture all of the sales that were licensed to different companies for a particular molecule. For the sub-sample of drugs for which this was an issue, we utilized the larger IMS worldwide sales values because they better captured the worldwide market.

Using this approach and these complementary data sources, we assembled worldwide sales data for 66 of the NCEs over the period of 1990 to 2000. We used a global multiplier approach for the remaining (very small selling) drugs in our sample. In particular, for these drugs, we multiplied their U.S. sales values times a representative global sales multiplier to obtain estimates of their worldwide sales.[9] As discussed, this latter sub-sample of drugs accounts for a very small share of overall sales for the full sample.

E. Life Cycle Sales Profiles

Given that the data were available for the years 1990 to 2000, this provided seven to eleven years of worldwide sales values for the NCEs in our sample, depending on their date of introduction into the U.S. market. The next task was to estimate future sales over the complete market life of these products. Twenty years was chosen as the expected market life. This is the same assumption that we utilized for 1980s new drug introductions. We believe this is a reasonable time horizon for an IRR analysis. Any sales remaining after 20 years of market life are likely to be very small, given the sales erosion experienced by most products from generic competition and product obsolescence. Furthermore, these sales will also be severely discounted by the cost-of-capital in an IRR analysis.

We utilized a two step procedure to project future sales values. These steps involve forecasting sales to the point of U.S. patent expiry and then projecting sales in the post patent period. The two-step approach is illustrated in Figure 1 for one of the products in our sample. This product was introduced into the U.S. market in 1992. There is nine years of sales information and its U.S. patent expiration occurs in year 12. By year 9, this product was in the mature portion of its product life cycle. Using a reference life cycle curve, the product is projected to have relatively stable sales (in constant dollar terms) until year 12.[10] A significant decline is then projected in the period after U.S. patent expiration due to the entry of generic competitors and related economic factors.

The estimated sales decline after patent expiry is based on the experience of major commercial products coming off patent in the 1994-97 period. In particular, we examined worldwide sales losses for a sample of NCEs for a four year period following their U.S. patent expiration. The average percentage decline observed were 31%, 28%, 20% and 20% respectively. We utilize these percentages to project sales in the first four years after patent expiration and thereafter, use a 20% percentage decline until the products market life is completed in year 20.[11]

We should note that the percentage declines in sales from generic competition in the U.S. market observed in prior studies are much greater than the worldwide losses in sales observed here.[16] Hence, the decline in worldwide sales in the post-patent period is ameliorated by the lower incidence of generic competition and sales losses outside the United States. This may change by the time this cohort actually reaches patent expiration during the current decade, because reference pricing and generic competition are on the rise in many European countries.[17]

Figure 2 provides a plot of the sales life cycle profile (in 2000 dollars) for top two deciles as well as the mean and median drug compounds in our 1990-94 sample. The sales curves illustrate the highly skewed distribution of sales in pharmaceuticals that was observed for early cohorts. The peak sales of the top decile compounds are several times the peak sales of the second decile compounds. The mean sales curve is also significantly above the median.

Figure 3 provides a plot of mean worldwide sales for the 1990s sample compared to that for the 1980s cohort (expressed in 2000 dollars). Mean sales have increased significantly in real terms, with peak sales increasing from $345 mil for the 1980s cohort to $458 mil for the 1990s cohort. There is also the suggestion that sales curves have become somewhat steeper in the ascending sales growth stages of the life cycle with a longer plateau before generic competition and product obsolescence takes hold.

Figure 4 shows a corresponding plot of the sales for the top decile compounds in the 1990-94 to 1980-84 periods. This is instructive given that the

prospective returns for top decile compounds are primary drivers of R&D investment activities in pharmaceuticals. For the 1990s cohort, the top decile compounds reached peak sales of over $2.5 billion. This may be compared to peak sales of near $1.8 billion for the 1980s cohort. The peak sales also occur later in time compared to the 1980s cohort.

F. Pre-Tax Contributions and Other Economic Parameters

The next step in the analysis is to obtain revenues net of production and distribution costs (often categorized in the economic literature as "quasi-rents"). For this purpose, we did an analysis of pre-tax contribution margins in pharmaceuticals during the 1990s. As in prior work we utilize data derived from the income statements of the pharmaceutical divisions of a number of major multinational drugs firms to obtain representative values on contribution margins over time.[1,2]

Our analysis of the data on these firms indicated that average contribution margins gradually increased from 42% in the early part of the 1980s to approximately 45% at the end of the decade. Based on these data, we constructed a linear contribution margin schedule over time. In particular, the contribution margin is 42% in the first year of the product life and grows by increments of 0.3% per year. We also assume that contribution margins will continue to rise at this same rate during the current decade. Hence, over the full 20-year life cycle, target contribution margins are expected to rise from 42% in year one, to 48% by year 20, with a mean contribution margin of 45%, over the full life cycle.

While we constrain margins to average 45% over the life cycle, we also recognize, as in our earlier analyses, that promotion and marketing expenditures are concentrated in the launch phases of the life cycle. In our prior analysis, we developed an allocation rule based on a regression analysis of promotional and marketing outlays. This rule was: promotion and marketing is equal to sales in year one, declines to 50% in year two, and falls to 25% in year three. We

retained this assumed pattern on marketing outlays in the present analysis. Interviews with industry participants indicated that the initial post-launch years continue to be the primary focus of marketing and promotion activities. An analysis performed by Rosenthal et al. [18] further indicates that the drug industry's marketing expenses to sales ratios have remained relatively stable in the 1996 to 2001 period.(12)

For the current analysis, we did make one relatively minor change in the allocation and timing of marketing expenditures related to launch. In particular, we estimated that pre-marketing launch expenditures will occur on the order of 5% and 10% of first year sales in the two years immediately prior to launch. These marketing expenditures are for activities such as pre-launch meetings and symposiums, pricing and focus group studies, and sales force training. Our assumptions concerning the size and timing of these expenditures were guided by a recent survey report on pre-launch marketing expenditures done by industry consultants as well as interviews with some of the participating companies.(13)

As indicated above, our model is structured so that margins average 45% over the full product life cycle. Given the assumed pattern of launch expenditures, contribution margins for each product are below representative industry values in the first three years of marketing. However, as a product matures, both promotional and administrative costs decline in relative terms, and contribution margins increase over average industry values in the later years of the life cycle.

The model is also structured to provide for capital expenditures on plant and equipment (P&E). As in our model for the 1980s cohort, we assumed overall capital expenditures for P&E to be equal to 40% of tenth year sales. Half of these outlays are assumed to occur in the first two years before marketing and the other half during the initial ten years of the product's market life. These assumptions imply an average capital investment to sales ratio of 3.3% over the full product life cycle. This is generally consistent with data from pharmaceutical industry income statements.(14)

For working capital, it was assumed that accounts receivables are equal to two months of annual sales and inventories are five months of sales (valued at manufacturing cost). These are also based on the analysis of balance sheet data of major pharmaceutical firms. Working capital is recovered at the end of the final year of product life.

G. Effective Tax Rates

Our analysis of returns is conducted on an after-tax basis. In our prior studies of returns, we computed average effective tax rates based on analysis of income statement data from eight major pharmaceutical firms. The average effective rate was 35% for the 1970s cohort and 33% for the 1980s cohort. A comparable analysis for the 1990s cohort yielded an effective tax rate of 30%. This is the rate that is used in our baseline case. The difference between the nominal corporate tax rate (34%) and the average effective tax rate of 30% reflects various credits and deferrals such as the R&D tax credit and manufacturing tax credits for plants in Puerto Rico.[2]

After-tax cash flows are also influenced by the tax treatment of depreciation. In our analysis, cash flow in each year is equal to after-tax profits, plus depreciation charges. Accelerated depreciation, as specified in the U.S. tax code, results in tax deferrals and positive cash flow in the early years of a product's market life. This reverses in the latter years of a product's life.

H. Summary of Economic Values

Table 2 provides a summary of the key economic inputs to IRR and NPV analysis for the 1990-94 NCEs cohort compared with the corresponding values for the 1980-84 cohort. R&D investment levels have roughly doubled in real terms, in both uncapitalized as well as capitalized dollar terms. On the revenue side of the equation, sales life curves have shifted upward significantly. This is

reflected in higher peak sales for the 1990-94 cohorts ($458 million compared to $345 million for 1980-84 NCEs). While sales have not grown at the same rate as R&D costs, contribution margins have increased in the 1990s implying higher operational profits from a given level of sales. How all these factors balance out from a returns-on-investment standpoint is a major issue addressed in the analysis which follows. The industry's cost-of-capital, effective tax rate, and capital investment to sales ratio have changed only marginally for the current cohort compared to the 1980s sample.

Table 2 suggests that R&D investment expenditures are growing over time relative to sales revenues and the other activities of pharmaceutical firms. This issue is discussed further in Section IV. This increase in industry research intensity can be interpreted both as a response to increasing profit opportunities from new drug research as well as an equilibrating factor bringing returns in line with the industry cost-of-capital. This makes the question of industry returns on new drug introduction in the 1990s a particularly interesting question to analyze at the present time.

III. Empirical Results

A. The Baseline Case

Using the data and assumptions described above, we constructed the pattern of cash flows for the mean of our sample of 118 NCEs shown in Figure 5. The R&D phase lasts for twelve years and results in a stream of negative cash flows. The first years of marketing, years 1 and 2, are also characterized by negative cash flows. This is because of heavy promotion and advertising expenditures during the product launch period. Cash flows rise to a peak in year twelve and then begin to decline. The decline becomes steeper as patent expiration and generic competition begin.

The baseline case results are shown in the first row of Table 3. The IRR is 11.5% and can be compared to our real Cost-of-Capital (COC) estimate of 11%. Hence, the industry mean performance is positive but only by a small amount. The present value of net revenues at the date of marketing is $525 million and can be compared to the present value of R&D costs at the same point in time, or $480 million. This leads to a Net Present Value (NPV) of $45 million.

The results for the baseline case for the 1990-94 NCEs are roughly the same as for our earlier 1980-84 sample. In the 1980-84 baseline case, the IRR was 11.1% compared to a COC of 10.5%. The 1990-94 IRR is similarly about a half percentage point above the COC estimate.

B. Sensitivity Analysis

Given the uncertainty surrounding many of the key parameters that affect the IRR and NPV, we have performed a sensitivity analysis for a number of the parameters. These results are reported in Table 3.

An important parameter is the contribution margin. As discussed earlier, we examined data for a number of firms during the 1990s and found that the average margin increased from 42% to 45%. We then projected a continuing increase in the margin until year 20. That is, we assumed that the margin increased from 42% to 48% by year 20, yielding an average of 45%. Hence, for the sensitivity analysis, we calculated the IRR and NPV for average margins of 40% and 50%--in both cases the upward trend of the base case was maintained. For example, for the lower margin case we assumed that the margin increased from 37% to 43% by year 20.

The IRR varied significantly from 10.6% to 12.4% as the average margin varied from 40% to 50%. Similarly the NPV ranged from a negative $32 million to $120 million. It should be noted that for the first ten years or so of product life the margin is based on real data—it is the last ten years that is more uncertain

and difficult to predict. Hence, the range of change in outcomes in perhaps overstated.

The next parameter that we examine in Table 3 is the tax rate. The base case is 30% and we calculate the effect of tax rates of 25% and 35%. Clearly, changing the tax rate results in quite small changes in the IRR and NPV. At 25% the IRR is 11.6% and at 35% it is 11.4%-- compared to the base IRR of 11.5%. This relative insensitivity of the IRR to the tax rate reflects the fact that this rate affects the R&D cost and revenue sides of the equation in a parallel fashion.

The effect of generic competition in eroding pioneer brand sales after patent expiration has tended to become greater over time. In the U.S., generic market shares in terms of pills sold increased from 35% one year after generic entry in the period immediately following the 1984 Hatch-Waxman Act to 64% in the mid 1990s.[6] Europe is also experiencing a rising trend in generic competition.[17] As a result, it is difficult to predict the degree of sales loss in the future. To examine this problem, we assumed two alternative scenarios: that the sales losses of the pioneers after patent expiration were 25% and 50% greater than what was assumed in the base case. Figure 6 shows these alternative sales erosion patterns.

Given that the effect of these sales losses occurs in the later stages of the product life cycle, the effect is made smaller when measured in present value terms. The IRR falls modestly from 11.5% in the base case to 11.4% and 11.3% in the 25% and 50% greater erosion cases respectively. Similarly, the NPV falls from $45 million in the base case to $33 million and $20 million.

Varying the COC results in significant changes in the NPVs. A 10% COC would result in a NPV of $131 million, considerably larger than the base case using the 11% COC of $45 million. A 12% COC, on the other hand, leads to a negative NPV of $37 million. These changes are comparable in magnitude to those observed for changes in the contribution margin.

The final sensitivity analysis in Table 3 is the effect of reducing regulatory review time by one year. This involves a change in the average regulatory review time from 18 months to 6 months. Our approach is to simply shorten the

R&D period by one year and compute the lower capitalized value of R&D at the date of marketing. This reduces R&D from $480.3 million to $437.7 million; hence, the base NPV rises from $45 million to $87.5 million. The IRR increases from 11.5% to 12.2%. These are clearly significant effects.[15]

C. Distribution of Returns

In figure 7, we show the decile distribution of present values of returns for the 1990-94 samples of NCEs. These returns are gross of R&D costs. The deciles are constructed based upon the ranking of the 118 NCEs in terms of their individual present values of returns. The average sales of the top decile of NCEs are then used to calculate the present value of returns for the top decile, and so forth.

The figure shows that the distribution is highly skewed. For example, the top decile has an estimated present value of $2.7 billion. This is almost six times the present value of average R&D costs ($480 million). The top decile alone accounts for about 52% of the total present value generated by all ten deciles. This compares to the value of 46% that we found in our 1980-84 study.

It is also true that the second and third deciles have present values that exceed average R&D costs, or $1 billion and $0.6 billion respectively. However, the fourth decile's present value is only $433 million in comparison to average R&D costs of $480 million. A detailed analysis of the present value for the individual NCEs shows that 34% or about one-third of the NCEs have present values in excess of the average R&D cost. By the time one gets to the median drug, present values are significantly below R&D costs.

A further illustration of the importance of top-ranked NCEs to industry returns can be demonstrated by removing the very top-ranked drug from the analysis. That is, we will eliminate Zocor, thereby reducing the sample from 118 to 117, and re-calculate the mean present value of returns. The result is that the present value falls from $525 million to $479 million, and the NPV falls from $45

million to a negative $1 million. Hence, if it were not for this one "blockbuster" drug, the average NCE of the 1990-94 cohort would essentially just break even in terms of an NPV analysis.

We should observe that the fact that the majority of the drugs in our sample have present values substantially below the fully allocated R&D cost does not mean that these drugs are not economically important. Since the average R&D cost includes an allocation for drugs that drop out during the development process, an "unprofitable" drug that more than covers variable costs going forward contributes positively to the firm's bottom line. Many of the uncertainties that exist for a new product (i.e., its clinical profile in terms of risks and benefits, the introduction of substitute products, the size of market demand, etc.), are usually not resolved until late in the R&D process. At this point, most of the R&D costs are sunk. Therefore, it is still worth getting the incremental revenues of these smaller selling drugs, if they can cover their expected variable costs going forward. Over the long run, however, a firm must have it share of products in the top few deciles to have a viable R&D program.

Figure 8 provides a comparison of the distribution of returns for all four sample cohorts that we have examined to date: 1970-74, 1975-79, 1980-84 and 1990-94. The vertical axis in this graph shows the percentage of overall returns that each decile accounts for in its sample cohort. The drug industry has exhibited a high degree of skewness over all 4 sample cohorts spanning this 25 year period. In this regard, the top decile has accounted for between 46% and 54% of the overall returns over the 4 sample cohort that we have analyzed. Scherer and colleagues have shown that a high degree of skewness is typical of several different populations of technological innovations, including the outcomes of venture backed startups, university licensed patents and venture backed companies in the initial period after their IPOs.[20]

IV. Drug Innovation and Industry Evolution Since 1970

As discussed in the Introduction, this is the third study that we have performed of the industry returns on R&D. The three studies employ the same general methodology. Consequently, they provide a convenient window to view the industry's development over the critical period from 1970 through the 1990s.

A. Trends in Industry Returns and R&D Expenditures

In Table 4, we provide a summary of the mean internal return observed for our sample beginning with the 1970-74 cohort and ending with the 1990-94 period. The first column in Table 1 shows that the IRR has increased steadily from 7% for the 1970-74 sample to 11.5% for 1990-94 introductions. The biggest incremental change occurred during the second half of the 1970s and the first half of the 1980s. Over this time period, the mean return increased from 7.0% to 9.7% and then to 11% respectively.

It is instructive to compare the mean estimated industry return in each period to the corresponding cost-of-capital (COC) for the pharmaceutical industry over that same period. For the 1970-74 cohort, the mean industry return of 7.0% was significantly less than the industry's cost-of-capital of 9%. This relationship reversed in the second half of the 1970s (with a 9.7% IRR versus a 9% COC). While the industry cost-of-capital increased in the 1980s and 1990s, so has mean returns. Returns have remained modestly above the cost-of-capital for these cohorts.

It is also useful to examine the trends in industry R&D expenditures during these periods. Figure 9 shows the aggregate R&D-to-sales ratios for seven major drug firms that have reported R&D consistently over the complete period 1962 to 1994.[21] This figure shows that the R&D-to-sales ratios for these firms declined in the period 1962 to 1974, stabilized in the second half of the 1970s,

and then began a steep increase from 1980 to 1994. The R&D-to-sales ratios for these firms grow from 7% in 1980 to 13% in 1994.

Mike Scherer has recently examined long term trends in industry R&D expenditures and profit margins for the period 1962 to 1996.[2] He finds a 0.96 rank correlation in the deviations from trends in this industry's expenditures and profit margins over this 35 year period. His results also indicate that R&D expenditures and profit margins in the pharmaceutical industry generally grow out a slower rate relative to the long run trend until the late 1970s, when they began a steep upward track.

These findings suggest that a beneficial competitive cycle may be at work in the pharmaceutical industry. In particular, R&D investment has not only led to innovation and profits in the form of the highly skewed distribution of returns observed here, but profits, or the expectation of profits, has produced expanding R&D investment. In this latter regard, Grabowski and Vernon also find that industry profit expectations on R&D, as well as internal cash flows, are highly significant explanatory variables of R&D investment outlays.[21] This type of competitive feedback cycle can be viewed as socially beneficial given the extensive literature on the high social returns from pharmaceutical R&D. [22] [23]

Scherer has characterized the strong relationship between industry R&D investment and profitability, in conjunction with the fact that mean industry returns are only modestly above the industry cost-of-capital, as evidence of a "virtuous rent seeking model." If this is a correct interpretation of the industry's competitive behavior, the data on long term trends suggests that the late 1970s represented a key turning point in terms of both industry returns and the growth in R&D expenditures. This issue is explored further in the next section.

B. The Pattern of Drug Innovation Since 1970

A number of pharmaceutical industry studies found diminishing returns to R&D characterized the 1960s and 1970s compared to the earlier post-War

period.[24, 25] The earlier period had witnessed a wave of important drug introductions. This involved many new antibiotic drugs, hydrocortisone and several other cortocoids, the thiazide diuretic and beta blocker drugs for hypertension, new classes of tranquilizers and anti-depressants, and the initial birth control drugs. However, by the early 1970s, the industry was experiencing diminishing returns in many of the drug classes that had seen major advances in the 1950s and 1960s. A number of hypotheses were investigated, including the effects of more stringent FDA regulations, diminishing technological opportunities and increased product liability. Some scholars saw the industry entering a prolonged period of technological maturity.[26]

Finding new drugs that were advances over established drugs had clearly become increasingly costly and more problematic by the early 1970s. Many of the leading firms began to focus their R&D activities on new therapeutic targets and approaches. One important concept that took root during this period was the "rational drug-design" approach to R&D. This involved the use of x-ray crystallography and other techniques to design specific compounds that could block particular receptor sites and thereby create desired therapeutic responses. The primary approach to discovering new drug therapies prior to this time involved the random screening of compounds against a small number of known targets.

An important milestone for the industry occurred in 1978 with the introduction of Tagamet (cimetidine) by SmithKline. This drug was not only a significant advance in the treatment of ulcers, but also provided validation of the "rational drug design" approach to R&D. Tagamet was the first of the histamine H_2 receptor inhibitors. It was specifically designed to block H_2 histamine receptors which were known to affect the process of acid secretion. Within a few years, it had become the largest selling drug worldwide. This drug by itself had a disproportionate effect on the returns for the full portfolio of 1970s new drug introductions. Indeed, when this one drug was removed from the portfolio of 1970-79 drugs, the average present value for the remaining compounds declined by 14%.[2] Tagamet was eventually replaced by another H_2 blocker, Zantac, as

the largest selling drug worldwide. Zantac became the top selling drug in our 1980-84 cohort of NCEs.[1]

The two and one-half decades that have elapsed since the introduction of Tagamet in 1978 have witnessed an impressive renaissance in drug innovation that is reflected in the trends toward higher returns and R&D intensities over this period. Table 5 provides a list of several important new chemical classes of drugs that were first introduced between 1978 and 1994. These classes all represent a new approach or mode of action to treating particular diseases or indications. The pioneering drugs in these classes are concentrated in the very top deciles of the sample cohorts for which we have analyzed returns. Many of these drugs have been the subject of specific cost benefit and pharmcoeconomic studies.

Table 5 also provides information on the various indications and disease categories to which these new drug classes are targeted. There are many diseases listed which previously had few or inadequate drug treatments (i.e., herpes, AIDS, ovarian cancer, migraine, schizophrenia, etc.). The list also includes several novel biotech drugs like Erythropoletin (used to treat anemia for patients undergoing treatment for kidney dialysis, AIDS and cancer) and the alpha and beta interferons used in the treatment of cancer and multiple sclerosis. Several of the new classes of drugs listed in Table 5 provide medical and economic benefits in the form of better patient tolerability and side effect profiles in the treatment of widespread medical problems (i.e., hypertension, cholesterol reduction, depression, etc.).

Looking forward, the drug industry is currently confronted with a new wave of technological opportunities. The mapping of the genome, and related advances in fields like bioinformatics, has led to an abundance of potential new targets for disease intervention. These advances could have profound effects on the discovery process itself, the size of clinical trials and the nature of demand for pharmaceutical products.[27] However, it remains unclear how fast these new technologies will result in important new drug therapies and how they will impact industry returns. In this regard, a recent report by McKinsey and Lehman

Brothers foresees a negative impact on returns until at least the latter part of this decade, when the substantial required buildup in R&D investments begin to bear fruit.[28] If this is so, the industry could be facing another crossroads in the immediate future as the transition to new R&D paradigms compounds already existing economic pressures from the health care sector, financial markets, and government officials.

V. Summary and Conclusions

Consistent with our prior studies, a primary finding of the current analysis is that the distribution of returns for 1990-94 new drug introductions is highly skewed. In this regard, only one-third of the new drug introductions had present values in excess of average R&D costs. The top decile of compounds by itself accounted for over 50% of the present value of post-launch returns generated by the full sample of introductions.

From an industry prospective, the estimated mean return for the 118 new drug introductions in the 1990-94 period was 11.5%. This compares to a real cost-of-capital of 11% for this sample cohort. At this cost-of-capital, the mean introduction earned an NPV of $45 million dollars (2000 dollars). A sensitivity analysis showed that returns are robust to changes in the economic parameters and assumptions. Changes in contribution margins and R&D times had the most impact on returns.

The principal results are, therefore, similar in nature to our study of 1980-84 new drug introductions – namely R&D in pharmaceuticals is characterized by a highly skewed distribution of returns and a mean industry IRR modestly in excess of the cost-of-capital. However, a look at the pattern of change on the inputs into our analysis shows a number of dynamic forces at work in this industry. In particular, R&D investments per new drug introduction approximately doubled compared to the 1980-84 period. At the same time, the number of new introductions, the average sales per introduction and industry contribution margins increased significantly in the 1990s compared to the 1980s.

Our studies of industry returns provide support for what has been labeled as a "virtuous rent seeking model" of R&D competition in the pharmaceutical industry. Since the end of the 1970s, the industry has experienced rapid growth in R&D outlays and the introduction of many important new therapeutic classes and blockbuster compounds. At the same time, mean industry returns on R&D over this period have only modestly exceeded the industry's cost-of-capital. Whether this beneficial cycle of increasing R&D intensities and innovative new product introductions will continue into the future remains to be seen. There are currently a number of promising new developments in the pharmaceutical R&D process, but the benefits from these technologies have an uncertain time horizon and they will likely require substantial increases in industry R&D investments. How quickly these evolving new technologies will lead to important new medicines will depend not only on scientific and economic factors, but also on the course of public policy actions.

FOOTNOTES

1. We are using a broad definition of NCE here. Our sample includes "large-molecule" biologics, in addition to traditional "small molecule" chemical drugs.

2. Three drugs were omitted from our sample because they failed to appear in any year in the IMS sales data audits. These three drugs involved an antiprotozal agent for sleeping sickness, an agent for opiate dependence, and one for nephropathic cystinosis, a rare inherited disorder affecting functioning of the liver. These products are apparently distributed outside of normal sales channels. In addition, given their special indications and characteristics, they are also likely to have non-representative R&D costs.

3. Another related fact is the passage of the Orphan Drug Act by Congress in 1983. This provided economic incentives, especially 7 years of market exclusivity, for the development of drugs targeted to indications involving less than 200,000 patients (or for which the manufacturer could demonstrate that development would be unprofitable). As we have discussed elsewhere, there is a high degree of overlap between the biopharmaceutical and orphan drug sub-samples.[8] This reflects the fact that many of the initial recombinant biotech drugs had indications for small patient populations and, in addition, biopharmaceutical firms sought out the market exclusivity protection of the Orphan Drug Act, given the uncertainties surrounding many biopharmaceutical patents.

4. Myers and Shyum-Sunder found that many pharmaceutical firms have large positive cash balances and are actually net lenders rather than net borrowers. Consequently, these firms have a negative debt ratio. Myers and Shyum-Sunder do a sensitivity analysis to gauge how this factor

would affect their 1990 value and they find it causes the nominal (and real cost-of-capital) to increase by almost a full percentage point.[9]

5 Several surveys have been performed of the hurdle rates used by U.S. companies. A general finding is that hurdle rates are typically greater than the weighted cost-of-capital computed by a CAPM analysis. For example, Poterba and Summers received responses from 228 companies, of the Fortune 1000, and found an average hurdle rate of 12.2% in real terms in the early 1990s.[12] They also found that hurdle rates can vary substantially across a company's functional areas and specific projects. The average difference between the highest and lowest hurdle rate within companies was 11.2%.

6. Myers and Howe further indicate that the R&D decision process can be modeled as a compound option pricing model.[11] Under this model, at any point in the R&D decision-making process, future R&D serves as a form of leverage, or debt, assuming the firm decides to undertake further development and marketing. Since this "debt" or leverage declines over the subsequent stages of the R&D process, so will the firm's cost-of-capital. Implementation of this model requires unobservable informational inputs compared to the standard CAPM approach using a weighted cost-of-capital. DiMasi et al, perform a sensitivity analysis using this option value approach, and show that for reasonable values of the forward looking discount rates, the CAPM and option value models yield comparable results.

7. Since our sample is centered around 1992, we utilize the following linear extrapolation equation to derive R&D costs:

$$R\&D_{92} = R\&D_{84} + (8/13)\ R\&D_{97}$$

8. DiMasi et al. obtained data from all the firms participating in his survey on pre-approval and post-approval R&D expenditures. Based on an analysis of these data, they estimated that out-of-pocket R&D expenditures for product extensions in the post-approval period were 34.8% of pre-approval R&D expenditures. Applying this percentage to our estimate of $308.4 million for pre-approval R&D yields an estimate of $107 million (in 2000 dollars) as the R&D cost for post-launch product improvements.

9. For these purposes, we utilized a global sales multiplier of 2.19 that was derived from actual worldwide sales and U.S. sales for the other drugs in our sample. This multiplier may overstate worldwide sales for drugs to which it is applied since, as noted, these drugs may well not have diffused globally as extensively as the drugs for which we had worldwide sales data.

10. The reference life cycle curve is based on observed sales for drug products introduced into the market in the immediately prior period. We used this as the basic template for most of the NCEs. However, we also make adjustments to these values using the sales projections of security analysts to allow for changing market conditions and competitive developments in particular therapeutic classes.

11. In our prior work on generic competition, we found that generic competition is focused on products with significant sales at the time of U.S. patent expiration. Consequently, for the drugs concentrated in the bottom four decile of our sample (with worldwide sales of less than 40 million dollars in year 10 of their market life), we assume that the probability of generic competition is very low. For these drugs we assume sales losses in the mature phase of cycle will proceed at a more moderately declining rate based on the reference curve used for the pre-patent expiration period.

12. Although the aggregate marketing to sales ratio in the U.S. pharmaceutical industry was stable around 14% between 1996 and 2000, there were some important compositional shifts over this period. Direct-to-consumer advertising to sales ratio increased from 1.2% to 2.2% between 1996 and 2000, at the expense of physician detailing and hospital medical journal advertising. The growth in direct-to-consumer advertising was stimulated, in part, by a change in the FDA regulations involving television ads for prescription drugs in 1997.[18]

13. Best Practices LLC, a Chapel Hill, NC management consulting firm, conducted interviews with and obtained data from 11 pharmaceutical firms on global marketing launch expenditures in 1998. In particular, they focused on 12 market launches in depth and obtained detailed marketing data relating to these launches. We talked with several of the participants in this study to get further perspective on how these budgeted expenditures generally related to first year sales. We used this information to develop the representative percentages used in the model.

14. In particular, we checked the reasonableness of our assumptions by comparing this implied 3.3% capital investment to sales ratio to the corresponding ratios observed on industry income statements during the 1990s. We found that the drug industry capital investment to sales ratio averaged about 7.0% during the 1990s. However, the latter value includes investment for R&D as well as production, marketing and administrative facilities. In our model, provisions for capital investment in R&D facilities are included in the cost estimates provided by DiMasi. Accordingly, we asked some industry members involved with strategic planning for information on what percentage of their plant and capital equipment expenditures were devoted to R&D, versus other firm activities. We obtained a range of 40 to 50% of total capital expenditures devoted to

R&D. Given this range, the capital investments to sales ratio for non-R&D activities implied by our model is consistent with the observed data from company income statements.

15. This sensitivity analysis captures only the direct effects of shorter FDA review times on the capitalized value of R&D costs. We abstract from any potential benefits associated with a longer effective patent life. As we have explained elsewhere, under the 1984 Hatch-Waxman Act, most drugs are eligible for compensatory increases in effective patent life equal to any lost time in regulatory review. Consequently, it is only for a smaller subset of drugs where the patent restoration time is constrained where shorter regulatory review times would increase effective patent life (for example, because there is a maximum of five years on the patent life restored under the Act). We abstract from these potential secondary benefits in the above sensitivity analysis.

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TABLE 1

Capitalized R&D Costs for Mean NCE in the 1990-94 Sample

R&D Costs (mils 2000$)	Pre-Tax	After-Tax
Discovery and Development	$613	$429
Product Extensions After Launch	73	51
Total	$686	$480

NOTES

1. R&D costs include expenditures on product failures as well as successes.

2. R&D costs are capitalized to the first year of marketing using an 11% cost-of-capital.

TABLE 2

Key Economic Values for IRR Analysis
1990-94 vs. 1980-84 NCEs

Average R&D Costs:	1990-94	1980-84
Pre-Tax Uncapitalized	$416 mil	$196 mil
After-tax Capitalized	$480 mil	$251 mil
Peak Sales for Mean NCE	$458 mil	$345 mil
Contribution Margin	45%	40%
Cost-of-Capital	11%	10.5%
Effective Tax Rate	30%	33%
Capital to Investment Sales Ratio	3.3%	3.4%

NOTES

A. R&D costs and sales values are all expressed in 2000 dollars.

B. Average contribution margins over the full product life cycle; launch costs are concentrated in early phases of life cycle, so margins are lower in initial years and higher in later years.

TABLE 3

Returns to 1990-94 NCEs

Case	Present Value Cash Flows (after-tax)	Present Value R&D Costs (after-tax)	NPV	IRR
Baseline	525.2	480.3	45.0	11.5
at 40% margin	449.8	480.3	(30.5)	10.6
at 50% margin	600.7	480.3	120.4	12.4
at 0.25 tax rate	571.3	514.6	56.7	11.6
at 0.35 tax rate	479.2	446.0	33.2	11.4
at 25% greater sales decline after patent life	512.9	480.3	32.7	11.4
at 50% greater sales decline after patent life	500.7	480.3	20.4	11.3
at 10% cost-of-capital	586.8	455.7	131.1	--
at 12% cost-of-capital	470.0	506.7	(36.8)	--
at 1-year reduction in regulatory review time	525.2	437.7	87.5	12.2

Baseline case assumes 11% cost-of-capital, tax rate of 0.30 and margin of 0.45.

TABLE 4

Mean Industry Returns and Cost-of-Capital for Diffect Time Cohorts of NCES

NCE Cohort	Mean IRR	Cost-of-Capital
1970-74	7.0%	9.0%
1975-79	9.7%	9.0%
1980-84	11.1%	10.5%
1990-94	11.6%	11.0%

TABLE 5

Important New Drug Classes
1978 – 94

Year	Class	Early Entrants	Indication
1978	H_2 receptor antagonists	Tagamet, Zantac	Ulcers
1981	ACE inhibitors	Capoten, Vasotec	Hypertension
1982	Calcium Channel Blockers	Procardia, Calan	Hypertension
1982	Nucleosides	Zovirax, Famvir	Herpes Virus
1983	Interleukin-2 inhibitors	Sandimmune	Transplantation
1985	Human Growth Hormones	Protropin, Humatrope	HGH Deficiency
1986	Quinolones	Noroxin, Cipro	Antibiotic
1986	Interferon Alphas	Intron A, Roferon A	Cancer
1987	Statins	Mevacor, Pravachol	Cholesterol Reduction
1987	Nucleoside/RT inhibitors	Retrovir, Videx	AIDS
1988	Serotonin Reuptake Inhibitors	Prozac, Zoloft	Depression
1989	Proton pump inhibitors	Prilosec, Prevacid	Ulcers
1990	Erythropoietin	Epogen, Procrit	Anemia
1990	Macrolides (semi-synthetic)	Biaxin, Zitromax	Antibiotic
1990	Bis-Triazoles	Diflucan	Antifungal
1991	5-HT_3 antagonists	Zofran, Kytril	Antiemetic
1992	Granulocyte (G-CSFs)	Neupogen	Cancer Adjunct
1993	Taxoids	Taxol, Taxoterre	Ovarian Cancer
1993	Interferon-betas	Betaseron, Avonex	Multiple Sclerosis
1993	5-HT_1 antagonists	Imitrex, Zomig	Migrane
1994	D_2/5HT_2 antagonists	Risperidal	Schizophrenia

FIGURE LEGENDS

Figure 1 Actual and projected sales values for a representative sample product.

Figure 2 Worldwide sales profiles of 1990-94 new drug introductions.

Figure 3 Comparison of sales curves for the mean drug in 1990-94 and 1980-84 samples.

Figure 4 Comparison of sales curves for top decile drugs in 1990-94 and 1980-84 samples.

Figure 5 Cash flows over the product life cycle: baseline case.

Figure 6 Alternative assumptions regarding sales erosion in the post-patent period.

Figure 7 Present values by decile for 1994 new drug introductions.

Figure 8 Present values by deciles for four samples of new drug introductions.

Figure 9 Aggregate R&D to Sales Ratios 1962-1994.

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The price of innovation: new estimates of drug development costs

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Abstract

The research and development costs of 68 randomly selected new drugs were obtained from a survey of 10 pharmaceutical firms. These data were used to estimate the average pre-tax cost of new drug development. The costs of compounds abandoned during testing were linked to the costs of compounds that obtained marketing approval. The estimated average out-of-pocket cost per new drug is US$ 403 million (2000 dollars). Capitalizing out-of-pocket costs to the point of marketing approval at a real discount rate of 11% yields a total pre-approval cost estimate of US$ 802 million (2000 dollars). When compared to the results of an earlier study with a similar methodology, total capitalized costs were shown to have increased at an annual rate of 7.4% above general price inflation.

JEL classification: L65; O31

Keywords: Innovation; R&D cost; Pharmaceutical industry; Discount rate; Technical success rates

1. Introduction

Innovations in the health sciences have resulted in dramatic changes in the ability to treat disease and improve the quality of life. Expenditures on pharmaceuticals have grown faster than other major components of the health care system since the late 1990s. Consequently, the debates on rising health care costs and the development of new medical technologies have focused increasingly on the pharmaceutical industry, which is both a major participant in the health care industry and a major source of advances in health care technologies.

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One of the key components of the discussion is the role of private sector pharmaceutical industry investments in R&D and an understanding of the factors that affect this process. Although the industry engages in many forms of innovation, in general the most significant is the discovery and development of new chemical and biopharmaceutical entities that become new therapies. Our prior research (DiMasi et al., 1991) found that the discovery and development of new drugs is a very lengthy and costly process. In the research-based drug industry, R&D decisions have very long-term ramifications, and the impact of market or public policy changes may not be fully realized for many years. From both a policy perspective, as well as an industrial perspective, it is therefore important to continue to analyze the components of and trends in the costs of pharmaceutical innovation.

In this paper we will build on research conducted by the current authors (DiMasi et al., 1991) and others on the economics of pharmaceutical R&D. As we described in our prior study, "Empirical analyses of the cost to discover and develop NCEs are interesting on several counts. First, knowledge of R&D costs is important for analyzing issues such as the returns on R&D investment. Second, the cost of a new drug has direct bearing on the organizational structure of innovation in pharmaceuticals. In this regard, higher real R&D costs have been cited as one of the main factors underlying the recent trend toward more mergers and industry consolidation. Third, R&D costs also influence the pattern of international resource allocation. Finally, the cost of R&D has become an important issue in its own right in the recent policy deliberations involving regulatory requirements and the economic performance of the pharmaceutical industry". In the decade that has followed the publication of our earlier study, these issues remain paramount. In addition, the congressional debates on Medicare prescription drug coverage and various new state initiatives to fill gaps in coverage for the elderly and the uninsured have intensified the interest in the performance of the pharmaceutical industry.

In the current study we are not attempting to directly answer the policy debates mentioned above. Rather, our focus is on providing new estimates of economic parameters associated with the drug development process. In particular, we concentrate on estimates of the costs of pharmaceutical innovation. Our prior estimates have been used by the Office of Technology assessment (OTA), the Congressional Budget Office (CBO), and various researchers to analyze policy questions such as the effects on R&D activities of health care financing reform or changes in intellectual property legislation related to the pharmaceutical industry.

The approach used in this paper follows our previous study (DiMasi et al., 1991) and the earlier work by Hansen (1979). Given the similarity in methodologies, we are able to compare our results in the current study with the estimates in the earlier studies to illustrate trends in development costs. All three studies used micro-level data on the cost and timing of development obtained through confidential surveys of pharmaceutical firms for a random sample of new drugs first investigated in humans by these firms. In the current study, the new drugs were first tested in humans anywhere in the world between 1983 and 1994. The reported development costs ran through 2000.Ultimately, we are interested in the expected cost of development per approved new drug. The uncertainties in the research and development process result in expenditures on many development projects that are not successful in producing a marketed product. However, to produce an estimate of expected cost for a marketed product, we must allocate the costs of the unsuccessful projects to those

that result in a marketed new product. The R&D process is lengthy, and as such it is important to know at what stage of development expenses occur. Viewed as an investment project, it is necessary to know both the amount of expenditures and the timing of these expenditures, since funds committed to R&D in advance of any returns from sales have both a direct and an opportunity cost. We used a unique database to estimate various cost parameters in the development process. Of particular concern is the estimation of the average pre-tax cost of new drug development, since we are interested in the resource costs of new drug development and how they have changed over time.

1.1. Previous studies of the cost of pharmaceutical innovation

A summary of early studies of the cost of drug development can be found in the authors' previous study (DiMasi et al., 1991) and in OTA (1993). In brief, the early studies were either based on a case study of a specific drug (usually ignoring the cost of failed projects) or relied on aggregate data. Since the R&D process often extends for a decade or more and the new drug development process often changes, it is difficult to estimate the cost of development from aggregated annual data. In contrast, the study by Hansen (1979) and the current authors' previous study (DiMasi et al., 1991) estimated development cost based on data supplied by firms for a representative sample of drug development efforts.

DiMasi et al. (1991) used data on self-originated new drugs to estimate the average cost of developing a new drug. They obtained data from 12 pharmaceutical firms on the research and development costs of 93 randomly selected new drugs that entered clinical trials between 1970 and 1982. From these data they estimated the average pre-tax out-of-pocket cost per approved drug to be US$ 114 million (1987 dollars). Since these expenditures were spread out over nearly a dozen years, they capitalized these expenditures to the date of marketing approval using a 9% discount rate. This yielded an estimate of US$ 231 million (1987 dollars). Measured in constant dollars, this value is more than double that obtained by Hansen for an earlier sample. DiMasi et al. (1991) also found that the average cost of the first two phases of clinical trials doubled between the first and second half of their sample. This led to the expectation that development costs would be higher in future samples.

Based on an analysis by Myers and Shyam-Sunder performed for the OTA, the OTA (1993) report noted that the cost-of-capital for the industry was roughly 10% in the early 1980s. This is moderately higher than the 9% used by DiMasi et al. (1991). The OTA also recalculated the DiMasi et al. (1991) numbers using an interest rate that varied over the life of the R&D cycle thereby raising the cost estimate by US$ 100 million in 1990 dollars.[1] The OTA presented both pre- and post-tax cost estimates.

[1] The OTA applied a range of discount rates that varied with the time to marketing approval. They chose 14% for the earliest stage R&D and 10% for development just prior to approval, with rates in between that declined linearly with time in development. This approach was meant to capture the essence of the risk-return staircase perspective expressed by Myers and others, and discussed below. The methodology described in Myers and Howe (1997) is actually quite different, but the OTA technique yielded results that would not be much different (for the same distribution of costs) than what one would have obtained with the correct methodology (Myers and Howe, 1997, p. 33).

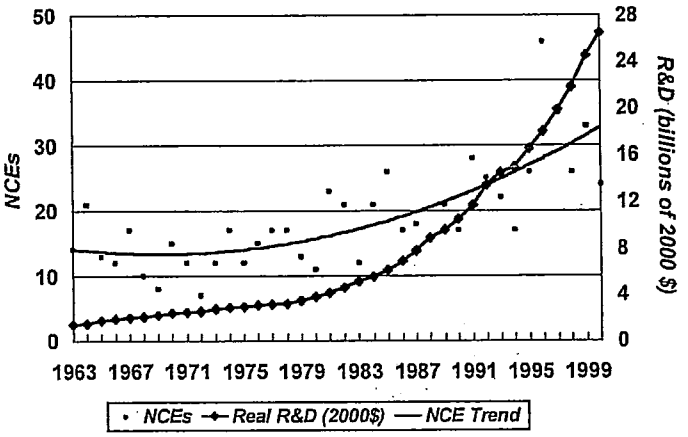

Fig. 1. Inflation-adjusted industry R&D expenditures (2000 dollars) and US new chemical entity (NCE) approvals from 1963 to 2000. Source of data: PhRMA (2001) and Tufts CSDD Approved NCE Database.

1.2. Aggregate data analyses

There have been no recent comprehensive studies of the cost of developing new pharmaceuticals from synthesis to marketing approval based on actual project-level data. However, aggregate data and data on parameters of the drug development process suggest that R&D costs have increased substantially since our earlier study. For example, the Pharmaceutical Research and Manufacturers of America (PhRMA, 2000) publishes an annual report on the R&D expenditures of its member firms that shows a continuous increase in outlays well in excess of inflation. Reports on specific components of the R&D process, such as the number of subjects in clinical trials (OTA, 1993; The Boston Consulting Group [BCG], 1993), also suggest an increase in the real cost of pharmaceutical innovation.

Published aggregate industry data suggest that R&D costs have been increasing. Fig. 1 shows reported aggregate annual domestic prescription drug R&D expenditures for members of the US pharmaceutical industry since 1963. The chart also shows the number of US new drug approvals by year. Given the much faster rate of growth of R&D expenditures, data such as these suggest that R&D costs have increased over time. However, they cannot be conclusive or precise. For one matter, the drug development process is known to be very lengthy. Thus, new drug approvals today are associated with R&D expenditures that were incurred many years prior. Ignoring the inherent lag structure underlying these data and simply dividing current R&D expenditures by the number of new drug approvals will in general yield inaccurate estimates.[2] Given a substantial increasing trend in R&D

[2] The estimates would also vary widely from year-to-year. For example, if we divided each year's real R&D expenditures by that year's number of NCE approvals, we would obtain US$ 1 billion for 2000, US$ 743 million for 1999, US$ 839 million for 1998, US$ 568 million for 1997, US$ 400 million for 1996, US$ 635 million for 1995, and US$ 878 million for 1994. While there is a general upward trend in such calculations, the year-to-year variability is not credible.

expenditures, such calculations will result in greatly exaggerated estimates of out-of-pocket cost per approval.

Secondly, even properly lagged time series would tend to be imprecise if aggregate industry data were used as reported. The industry data include expenditures on improvements to existing products. Thus, they would overestimate pre-approval development costs. On the other hand, they also do not incorporate all of the R&D on licensed-in drugs since firms or other organizations that are not members of the US trade association would have conducted some of the work. On that account the data would tend to underestimate costs. Therefore, R&D cost estimates based on project-level data are needed to assure a reasonable level of confidence in the accuracy of the results. We present results based on such data in this study.

The remainder of this paper is organized as follows. Section 2 describes the standard drug development paradigm, which serves as the structure through which the results are reported. Section 3 contains a description of the survey sample data and the population from which it was drawn. Section 4 describes the methodology used to derive R&D cost estimates. We present our base case pre-marketing approval R&D cost estimates in Section 5, as well as a comparison of our results with those of earlier studies to examine R&D cost trends. Section 6 provides sensitivity analyses for key parameters. Section 7 focuses on some extensions of the base case analyses: estimates of clinical development costs for approved drugs by therapeutic significance, estimates of post-approval R&D costs, and a tax analysis. Section 8 contains data and analyses that corroborate our results. Finally, we offer some conclusions in Section 9.

2. The new drug development process

New drug development can proceed along varied pathways for different compounds, but a development paradigm has been articulated that has long served well as a general model. The paradigm is explained in some detail elsewhere (DiMasi et al., 1991; US Food and Drug Administration [FDA], 1999). In outline form, the paradigm portrays new drug discovery and development as proceeding in a sequence of (possibly overlapping) phases. Discovery programs result in the synthesis of compounds that are tested in assays and animal models. It was not possible to disaggregate our data into discovery and preclinical development testing costs,[3] so for the purposes of this study discovery and preclinical development costs are grouped and referred to as preclinical costs.

Clinical (human) testing typically proceeds through three successive phases. In phase I, a small number of usually healthy volunteers[4] are tested to establish safe dosages and to gather information on the absorption, distribution, metabolic effects, excretion, and toxicity of the compound. To conduct clinical testing in the United States, a manufacturer must first

[3] The reported basic research expenditures by firm were highly variable, and suggest that different firms may categorize their pre-human testing expenditures somewhat differently. Thus, we report pre-human testing costs in one figure.

[4] In some therapeutic areas, testing is initially done on patients who have the disease or condition for which the compound is intended to be a treatment. This is ordinarily true in the cancer and AIDS areas.

file an investigational new drug application (IND) with the FDA. However, initiation of human testing can, and often does, occur first outside the United States.

Phase II trials are conducted with subjects who have the targeted disease or condition and are designed to obtain evidence on safety and preliminary data on efficacy. The number of subjects tested in this phase is larger than in phase I and may number in the hundreds. The final pre-approval clinical testing phase, phase III, typically consists of a number of large-scale (often multi-center) trials that are designed to firmly establish efficacy and to uncover side-effects that occur infrequently. The number of subjects in phase III trials for a compound can total in the thousands.

Once drug developers believe that they have enough evidence of safety and efficacy, they will compile the results of their testing in an application to regulatory authorities for marketing approval. In the United States, manufacturers submit a new drug application (NDA) or a biological license application (BLA) to the FDA for review and approval.

3. Data

Ten multinational pharmaceutical firms, including both foreign and US-owned firms, provided data through a confidential survey of their new drug R&D costs.[5] Data were collected on clinical phase costs for a randomly selected sample of the investigational drugs of the firms participating in the survey.[6] The sample was taken from a Tufts Center for the Study of Drug Development (CSDD) database of investigational compounds. Cost and time data were also collected for expenditures on the kind of animal testing that often occurs concurrently with clinical trials.[7] The compounds chosen were all self-originated; that is, their development up to initial regulatory marketing approval was conducted under the auspices of the surveyed firm.[8] Licensed-in compounds were excluded because non-survey firms would have conducted portions of the R&D.[9]

We also collected data from the cost survey participants on their aggregate annual pharmaceutical R&D expenditures for the period 1980–1999. The firms reported on total annual R&D expenditures broken down by expenditures on self-originated new drugs, on licensed-in or otherwise acquired new drugs, and on already-approved drugs. Annual expenditures on self-originated new drugs were further decomposed into expenditures during the pre-human and clinical periods.

The National Institutes of Health (NIH) support through their own labs and through grants to researchers in academic and other non-profit institutions a substantial amount of research

[5] Using pharmaceutical sales to measure firm size, four of the survey firms are top 10 companies, another four are among the next 10 largest firms, and the remaining two are outside the top 20 (PJB, 2000).

[6] A copy of the survey instrument is available upon request.

[7] Long-term teratogenicity and carcinogenicity testing may be conducted after the initiation of clinical trials.

[8] This does not preclude situations in which the firm sponsors trials that are conducted by or in collaboration with a government agency, an individual or group in academia, a non-profit institute, or another firm.

[9] Large pharmaceutical firms much more often license-in than license-out new drug candidates. Firms that license-in compounds for further development pay a price for that right through up-front fees, milestone payments, and royalty arrangements.

that expands fundamental knowledge about human biology (NIH, 2000; Scherer, 2000). This basic research sometimes results in leads that industrial researchers can capitalize on to assist them in discovering new therapeutic compounds.[10] Some new compounds investigated by pharmaceutical firms, however, originated in government or academic labs. It is unclear whether the discovery and early development costs for such compounds are similar to those for compounds originating in industrial labs. These drugs, though, represent a very small portion of the total number developed. For example, NIH (2000) found that of 47 FDA-approved drugs that had reached at least US$ 500 million in US sales in 1999, the government had direct or indirect use or ownership patent rights to only four of them.[11] In addition, we used a Tufts CSDD database supplemented by commercial databases to determine that of the 284 new drugs approved in the United States from 1990 to 1999,[12] 93.3% originated from industrial sources (either from the sponsoring firm or from another firm from which the compound was licensed or otherwise acquired). Government sources accounted for 3.2% of these approvals and academia and other non-profits accounted for the other 3.5%.[13]

The survey firms accounted for 42% of pharmaceutical industry R&D expenditures.[14] The survey compounds were selected at random from data contained in the Tufts CSDD database of investigational compounds for the firms that agreed to participate in the R&D cost survey. Of the 68 compounds chosen, 61 are small molecule chemical entities, four are recombinant proteins, two are monoclonal antibodies, and one is a vaccine. Initial human testing anywhere in the world for these compounds occurred during the period 1983–1994. Development costs were obtained through 2000.[15]

[10] The NIH also supports the development of research tools that drug developers find useful. In addition, it funds training for many scientists, some of whom eventually are employed in the industrial sector.

[11] The four drugs were developed in part through the use of NIH-funded patented technologies. Three of the four products are recombinant proteins, with two being the same drug produced by two different companies. Each of the relevant patented technologies was developed at academic or non-profit institutions with financial support from the NIH.

[12] The definition of a new drug used for this analysis is a therapeutic new molecular entity approved by the FDA's Center for Drug Evaluation and Research.

[13] The proportion of investigational drugs that derive from industrial sources is likely to be even higher, since acquired drugs have higher clinical approval success rates than do self-originated drugs (DiMasi, 2001b). Our cost survey firms were less reliant on licensing-in drugs from non-industrial sources than were firms as a whole; 98.8% of their new drug approvals during 1990–1999 were from industrial sources. DiMasi (2000) found markedly greater market entry of small niche pharmaceutical firms in the 1990s relative to earlier periods as measured by sponsorship of new chemical entity (NCE) approvals. A disproportionate share of the approvals obtained by these new entrants was for drugs that originated in academia.

[14] The data used were aggregate firm pharmaceutical R&D expenditures for the cost survey firms, as reported on our questionnaire, in comparison to PhRMA member firm R&D expenditures (1994–1997) on ethical pharmaceuticals, adjusted to global expenditure levels (PhRMA, 2001).

[15] Surveys were sent to 24 firms (some of whom have since merged). Twelve firms responded that they would participate in some form. The data that two firms ultimately provided were not useable. The 10 firms from which we used data provided information on 76 compounds. However, the data for eight of these compounds were not sufficiently comprehensive to use. The firms that did not participate in the survey cited a number of reasons for not doing so. The reasons included the extra demands that the transition effects of a relatively recent merger were placing on their relevant personnel, the time and expense of retrieving archival records in the manner required by the study, and difficulties in gathering the relevant data in a uniform manner because their accounting systems had changed significantly over the study period.

We selected a stratified random sample of investigational compounds. Stratification was based on the time elapsed since the origination of clinical trials and the current status of that testing. Reported costs were weighted to reflect the characteristics of the population, so that knowledge of the population from which the sample was drawn was needed. The population is composed of all investigational compounds in the Tufts CSDD investigational drug database that met study criteria: the compounds were self-originated and first tested in humans anywhere in the world from 1983 to 1994, and we had the information necessary to classify them according our strata. We found 538 investigational drugs that met these criteria. Of these compounds, 82 (15.2%) have been approved for marketing, 9 (1.7%) had NDAs or BLAs that were submitted and are still active, 5 (0.9%) had NDAs or BLAs submitted but abandoned, 227 (42.2%) were terminated in 4 years or less from the initiation of clinical trials, 172 (32.0%) were terminated more than 4 years after the start of clinical testing, and 43 (8.0%) were still in active testing as of the most recent check (31 March 2001).

Some firms were not able to provide full phase cost data for every new drug sampled. For example, phase I cost data were available for 66 of the 68 new drugs. However, we had some phase cost data for every drug in the sample. In addition, five compounds were still active at the time of the study. For these drugs it is possible that there will be some future costs for the drug's most recent phase. Thus, for this reason our cost estimates may be somewhat conservative. However, given the small number of drugs in this category and the fact that the impact would be on only one phase for each of these drugs, our overall cost estimates are not likely to be materially affected.

4. Methodology for estimating new drug development costs

The approach that we use to estimate development costs is similar to that described in our earlier work (DiMasi et al., 1991). We will outline here the general methodology for developing an overall cost estimate. In describing the approach, it will be clear that cost estimates for important components of the drug development process will also be derived along the way.

The survey sample was stratified to reduce sampling error. Results from previous analyses suggested that the variability of drug costs tends to increase with the development phase or the amount of time that a drug spends in testing (Hansen, 1979; DiMasi et al., 1991). Costs for successful drugs (i.e. those that achieve regulatory approval) also tend to be higher and more variable than those for drug failures. Thus, we based our strata on the length of time that failed compounds were in clinical testing and whether or not a compound had reached the stage in which an application for marketing approval had been filed with the FDA.[16]

[16] Specifically, we used four strata: compounds that failed in 4 years or less of clinical testing; compounds that failed after more than 4 years had elapsed from initial human testing; compounds for which an NDA or a BLA had been submitted to the FDA; and compounds that were still in active testing (as of 30 March 2001). Compounds for which an application for marketing approval had been submitted or which had been abandoned after lengthy testing were deliberately oversampled. The reported sample values were then weighted, where the weights were determined so that the sample perfectly reflects the population in terms of the four strata.

4.1. Expected costs in the clinical period

Since new drug development is a risky process, with many compounds failing for every one that succeeds, it is necessary to analyze costs in expected value terms. The total clinical period cost for an individual drug can be viewed as the realization of a random variable, c. Given that it is not certain that development of a randomly selected investigational compound will proceed to a given phase, we may define expected clinical costs for a randomly selected investigational drug to be $C = E(c) = p_{\mathrm{I}}\mu_{\mathrm{I|e}} + p_{\mathrm{II}}\mu_{\mathrm{II|e}} + p_{\mathrm{III}}\mu_{\mathrm{III|e}} + p_{\mathrm{A}}\mu_{\mathrm{A|e}}$, where p_{I}, p_{II}, and p_{III}, are the probabilities that a randomly selected investigational compound will enter phases I–III, respectively, p_{A} the probability that long-term animal testing will be conducted during the clinical trial period, and the μ's are conditional expectations. Specifically, $\mu_{\mathrm{I|e}}$, $\mu_{\mathrm{II|e}}$, $\mu_{\mathrm{III|e}}$, and $\mu_{\mathrm{A|e}}$ are the population mean costs for drugs that enter phases I–III, and clinical period long-term animal testing, respectively.

Weighted mean phase costs derived from the cost survey data were used to estimate the conditional expectations. A description of how the probabilities were estimated is presented in the next section. Assuming that the estimated mean phase costs and success probabilities are stochastically independent, the estimated expected value is an unbiased estimate of the population expected value.

4.2. Clinical success and phase attrition rates

An overall clinical approval success rate is the probability that a compound that enters the clinical testing pipeline will eventually be approved for marketing. Attrition rates describe the rate at which investigational drugs fall out of testing in the various clinical phases. A phase success rate is the probability that a drug will attain marketing approval if it enters the given phase. A phase transition probability is the likelihood that an investigational drug will proceed in testing from one phase to the next. All of these probabilities can be estimated from data in the Tufts CSDD database of investigational drugs from which our survey sample was drawn.

The clinical approval success rate was estimated using a two-stage statistical estimation process that has been described in detail elsewhere (DiMasi et al., 1991; DiMasi, 2001b). The data used here consist of the investigational drugs in the Tufts CSDD database that were first tested in humans anywhere in the world from 1983 to 1994, with information on their status (approval or research abandonment) obtained through early 2001. Given that some of these investigational drugs were still in active testing at the end of the study period, some of the data are right-censored. Survival analysis can be applied in such a situation, where survival indicates that a drug has not reached its ultimate fate (either approval or abandonment).

The Tufts CSDD database of investigational compounds contains information on the latest phase that an abandoned compound was in when it was terminated. These data were used to determine the distribution of research terminations by phases.[17] These results,

[17] A small proportion of the compounds in the database were either still in clinical development (8.0%) or had an NDA or BLA filed but not yet approved (1.7%). For those drugs in these groups that will eventually fail, their abandonment will tend to occur in later testing phases. To deal with the potential bias in the estimated distribution of research terminations that would result from using just those compounds that had been abandoned by the end of

together with the estimated overall clinical approval success rate were used to provide estimates of the probability that an investigational drug will enter a given phase, phase attrition rates, and phase transition probabilities. The estimated overall clinical approval success rate and the probabilities of entering various phases provide results with which estimates can be derived that include the cost of drugs that fail to make it through the development process. Specifically, we use the probabilities of entering a phase to estimate the expected out-of-pocket clinical cost per investigational drug. Adding the out-of-pocket preclinical cost estimate described below yields an estimate of total out-of-pocket cost per investigational drug. Dividing this estimate by the overall clinical success rate yields our estimate of out-of-pocket cost per approved drug.

4.3. *Out-of-pocket discovery and preclinical development costs*

Many costs incurred prior to clinical testing cannot be attributed to specific compounds. Thus, aggregate level data at the firm level were used to impute costs per drug for R&D incurred prior to human testing. Specifically, time series data for each surveyed firm on spending on pre-human R&D and on human testing for 1980–1999 were obtained, and a ratio of pre-human R&D expenditures to human testing expenditures was determined based on an appropriate lag structure (on average, pre-human R&D expenditures should occur years prior to the associated human testing costs). This ratio was then multiplied by an estimate of out-of-pocket clinical cost per drug, which is based on the project-level data, to yield an estimate of the pre-human R&D cost per new drug.[18]

4.4. *Capitalized costs: development times and the cost-of-capital*

Given that drug development is a very lengthy process, the full cost of drug development should depend significantly on the timing of investment and returns. Full cost estimates require a capitalization of the stream of out-of-pocket costs to some point (the date of marketing approval is the standard). To do so, one needs a timeline for a representative drug. The timeline is constructed from information on average phase lengths and the average gaps and overlaps between successive phases in a Tufts CSDD database of approved new drugs and in our cost survey. The periods considered are the time from synthesis to human testing,

the study period, we statistically predicted whether each open compound (still in clinical testing) would eventually fail. To do so, we evaluated an estimated conditional approval probability function (probit specification) at the number of years that the compound had been in testing. Failures were taken to occur in the latest reported testing phase. Summing the failure probabilities by phase gives us additional terminations by phase. The distribution of research terminations by phase was adjusted accordingly. Compounds that had reached the NDA/BLA phase likely have a very high probability of success. DiMasi (2001a) found very high approval rates for NDA submissions, with an increasing trend. To be conservative, we assumed that all of the compounds with still active NDAs or BLAs would be approved. This leads to lower cost estimates than would be the case if the same procedure for determining failure that was used for compounds still in testing had been used instead. However, given the very small number of compounds in the active NDA/BLA category, the impact on the results is trivial.

[18] The survey firms were asked to indicate whether charges for corporate overhead unrelated to R&D appear in their R&D budget data, and, if so, to estimate what share of expenditures they represent. Two firms reported that they did, and so we reduced the aggregate and project-level data for those firms according to their reported shares for corporate overhead.

the three clinical phases, an animal testing phase concurrent with clinical development, and the length of time from submission of an NDA/BLA to NDA/BLA approval.

Whereas the survey data cover a development period that yielded approvals from 1990 to 2001, the bulk of the approvals occurred in the mid to late 1990s. Thus, we estimated phase lengths, gaps, and overlaps for self-originated new drugs that were approved during 1992–1999. The data included therapeutic biopharmaceuticals, as well as small molecule drugs.[19] Once a timeline is established and out-of-pocket costs are allocated over that timeline, the expenditures must be capitalized at an appropriate discount rate. The discount rate should be the expected return that investors forego during development when they invest in pharmaceutical R&D instead of an equally risky portfolio of financial securities. Empirically, such a discount rate can be determined by examining stock market returns and debt-equity ratios for a representative sample of pharmaceutical firms over a relevant period. The resulting discount rate is an average company cost-of-capital. We describe the estimation of our base case cost-of-capital in Section 5.2 below.

We assume that phase costs are distributed uniformly over the phase length and apply continuous compounding to the point of marketing approval. Summing these capitalized preclinical and clinical capitalized cost estimates yields a total capitalized cost per investigational drug. Dividing by the overall clinical success rate results in our estimate of the total capitalized cost per approved new drug. This estimate is a measure of the full resource cost needed, on average, for industry to discover and develop a new drug to the point of marketing approval.

5. Base case R&D cost estimates

5.1. *Out-of-pocket clinical cost per investigational drug*

Given the method of weighting reported costs as described in Section 4, weighted means, medians, and standard deviations were calculated and are presented in Table 1.[20] Mean

[19] The percentage of all self-originated new compound approvals that are for biopharmaceuticals is substantially larger than is the proportion of either self-originated approvals or investigational compounds that are for biopharmaceuticals in the Tufts CSDD investigational drug database. The survey firms in this database are predominantly traditional pharmaceutical firms. Thus, we estimate clinical phase lengths and approval phase times for new chemical entities and biopharmaceuticals separately and compute a weighted average of the mean phase lengths, where the weights are the shares of self-originated investigational compounds in the Tufts CSDD database for each of these compound types.

[20] For five of the sample drugs, the survey firms were not able to disaggregate costs for two successive clinical phases (i.e. either phases I and II or phases II and III). We developed a two-stage iterative process for imputing phase costs for these drugs. To illustrate, suppose that the firm combined phases II and III costs for a specific drug. For a year during which the drug was in both phase II and III testing, let m_{II} = number of months the drug was in phase II only, m_{III} = number of months the drug was in phase III only, m_0 = number of months the drug was in both phases, T = total clinical phase cost for the drug during the year, and cr = ratio of weighted monthly phase III to phase II cost for drugs where phase costs were disaggregated. Imputed phase II cost, x_{II}, can then be defined as $x_{II} = (m_{II} + \text{cr} \cdot m_0)T/(m_{II} + \text{cr} \cdot m_{III} + [1 + \text{cr}] \cdot m_0)$. Imputed phase III cost is determined as $x_{III} = \text{cr} \cdot x_{II}$. The same approach was used when phase I and II costs were combined by the responding firm. To further refine the results, we included the imputed costs for the five drugs from the first stage and recomputed the phase cost ratios to determine second stage values for the imputed costs. The results for imputed costs barely changed between the first and the second iterations.

Table 1
Average out-of-pocket clinical period costs for investigational compounds (in millions of 2000 dollars)[a]

Testing phase	Mean cost	Median cost	Standard deviation	N[b]	Probability of entering phase (%)	Expected cost
Phase I	15.2	13.9	12.8	66	100.0	15.2
Phase II	23.5	17.0	22.1	53	71.0	16.7
Phase III	86.3	62.0	60.6	33	31.4	27.1
Long-term animal	5.2	3.1	4.8	20	31.4	1.6
Total						60.6

[a] All costs were deflated using the GDP Implicit Price Deflator. Weighted values were used in calculating means, medians, and standard deviations.
[b] *N*: number of compounds with full cost data for the phase.

cost per investigational drug entering a phase increases substantially by clinical phase, particularly for phase III, which is typically characterized by large-scale trials. In comparison to the previous study (DiMasi et al., 1991), mean phase I cost is moderately higher relative to the other phases. While the ratio of mean phase III cost to mean phase I cost was 6.0 for the previous study, it was 5.7 here. Similarly, the ratio of mean phase II to phase I cost was 1.9 for the earlier study, but was 1.5 for this study. The higher relative phase I cost is consistent with other data that indicate that the growth in the number of procedures per patient was much greater for phase I than for the other phases during the 1990s.[21]

Mean clinical phase costs increased approximately five-fold in real terms between the studies. However, in comparison, long-term animal testing costs incurred during the clinical period increased by only 60%. Thus, increases in out-of-pocket clinical period costs were driven heavily by increases in human trial, as opposed to animal testing, costs. This suggests that preclinical animal studies may also have not increased at anywhere near the same rate as have clinical trial costs. The results also indicate that development costs have become more uniform across drugs.

This is indicated by two comparisons with the results from the previous study. The ratio of mean to median phase cost decreased 50% for phase I, 22% for phase II, and 13% for phase III for the present study in comparison to the earlier study. Thus, the data are less skewed. The coefficients of variation for the phases also declined. They are 60% lower for phase I, 29% lower for phase II, and 36% lower for phase III.

Estimates of the probability that an investigational drug will enter a phase were obtained from statistical analysis of information in the Tufts CSDD database of investigational compounds for drugs that met study criteria. They are shown in Table 1 and are used to obtain the expected phase costs in the last column. The probabilities are lower in comparison to the previous study (75.0% for phase II, 36.3% for phase III, and 56.1% for long-term animal testing). Lower probabilities of entering a phase will, other things being equal, result in lower expected costs. Thus, while the mean phase costs for drugs entering a phase are

[21] One of the authors obtained data from DataEdge, LLC on the number of procedures administered to patients by phase from 1990 to 1997. The data were based on information in the clinical trial grants of a very large number of pharmaceutical firms. During this period, the number of procedures per patient increased 27% for phase III, 90% for phase II, and 120% for phase I.

approximately five times higher in this study, the expected cost per investigational drug is only four times higher.

Alternative probability estimates for the same data make clear how reductions in drug development risks hold down development costs. Our earlier study showed proportionately fewer failures in phase I (32.5% versus 37.0%) and proportionately more failures in phase III (17.1% versus 12.6%); the share for phase II was identical. Thus, given a similar overall clinical success rate, the evidence suggests that over time firms became better able to weed out failures (clinical or economic) early in the process. A similar scenario holds when we examine phase transition probabilities. In the earlier study, a larger percentage of investigational drugs made it to phase II (75.0% versus 71.0%) and a smaller percentage proceeded from phase III to marketing approval (63.5% versus 68.5%).

5.2. Cost-of-capital estimates

In our earlier paper (DiMasi et al., 1991), we employed a 9% real cost-of-capital based on a capital asset pricing model (CAPM) analysis for a representative group of pharmaceutical firms during the 1970s and early 1980s. A real rather than a nominal cost-of-capital is appropriate in our analysis since R&D costs are expressed in constant 2000 dollars. The real cost-of-capital in pharmaceuticals has increased since the mid-1980s primarily as a result of higher real rates of return required by holders of equity capital during the 1990s.

In the present analysis, we compute a weighted cost-of-capital for each firm in a representative group of pharmaceutical firms for the 1980s and 1990s, where the weights are based on the firm's market value of debt and equity. For most major pharmaceutical firms, debt securities account for less than 10% of market valuation, so that the equity cost-of-capital component is the dominant element of the weighted cost-of-capital for this industry. At the request of the OTA, Myers and Shyam-Sunder (1996) estimated the cost-of-capital for the pharmaceutical industry during the 1970s and 1980s using a standard CAPM approach. Their methodology is the basis for our updated analysis.

In our R&D cost analysis we have a sample of new drugs that began clinical trials in the mid-1980s through the early 1990s, and which have an average market introduction point in the late 1990s. Hence a relevant time period for our cost-of-capital measure is 1985–2000. Accordingly, we estimated the cost-of-capital at roughly 5-year intervals beginning in January 1985 and ending in January 2000. The results of our analysis are summarized in Table 2.

The nominal cost-of-capital in 1985 and 1990 are based on Myers and Shyam-Sunder's analysis for the OTA. The 1994 value is from Myers and Howe (1997). The 2000 nominal cost-of-capital (COC) value is based on our own estimation, employing a sample of firm and data sources comparable to those used in the prior work of Myers and colleagues. As can be seen in Table 2, the nominal cost-of-capital for pharmaceutical firms has remained relatively stable in this period in the range of 14–16%, with a mean of approximately 15%.[22]

[22] We undertook an informal survey of major pharmaceutical firms in mid-2001 with respect to the hurdle rate that they used in their R&D investment decisions. This survey of six firms yielded (nominal) hurdle rates from 13.5 to over 20%. This indicates that a 15% nominal COC rate is within the range of hurdle rates utilized by major pharmaceutical firms for their actual R&D investments.

Table 2
Nominal and real cost-of-capital (COC) for the pharmaceutical industry, 1985–2000

	1985	1990	1994	2000
Nominal COC (%)[a]	16.1	15.1	14.2	15.0
Inflation rate (%)[b]	5.4	4.5	3.1	3.1
Real COC (%)	10.8	10.6	11.1	11.9

[a] The nominal values for 1985 and 1990 are based on Myers and Shyam-Sunder (1996). The nominal value for 1994 is taken from Myers and Howe (1997). The 2000 nominal value is based on our own computations using comparable samples and data sources.

[b] The inflation rate for 1985 is taken from Myers and Howe (1997), the rate for 1990 is a 5-year average centered on January 1990 and is based on the CPI-U, the rate for 1994 and 2000 is the long-term inflation rate from 1926 to 2000 (Ibbotson Associates, 2001, p. 17).

To obtain a real cost-of-capital, we subtracted the expected rate of inflation from the nominal cost-of-capital. For this purpose, Myers and Shyam-Sunder (1996) used the expected rate of inflation from a special consumer survey performed in the 1980s. We also used this value in Table 2 for the 1985 period. For 1990 we utilized a 5-year moving average of actual inflation rates centered around the year in question to estimate expected rates of inflation. For 1994 and 2000 we used the long-term inflation rate (1926–2000) in Ibbotson and Associates (2001) of 3.1% to compute the values in Table 2.[23]

The real cost-of-capital for the pharmaceutical industry over this period, using the CAPM model, varies from 10.6 to 12.0%. The mean cost-of-capital in this period was just over 11%. Hence, 11% is the baseline value that we employed in our R&D cost estimates.[24] However, as in prior studies, we did sensitivity analysis around this value in order to determine how our baseline R&D cost estimates are affected by changes in the cost-of-capital.

5.3. *Capitalized clinical cost per investigational drug*

To calculate opportunity cost for clinical period expenditures we estimated average phase lengths and average gaps or overlaps between successive clinical phases. Mean phase lengths and mean times between successive phases are shown in Table 3. The time between the start of clinical testing and submission of an NDA or BLA with the FDA was estimated to be 72.1 months, which is 3.5 months longer than the same period estimated in the previous study. However, the time from the start of clinical testing to marketing approval in our timeline for a representative drug averaged 90.3 months for the current study, compared to

[23] Inflation rates were particularly low in the 1990s, and 5-year moving averages were below the long-term rate. Since the 1990s represented a marked change in the inflation rate from earlier decades, and inflationary expectations may not adjust immediately to the new experience, we used the long-term inflation rate rather than 5-year moving averages for this period.

[24] This yields conservative estimates of the cost of capital from several perspectives. One important point concerns the fact that many major pharmaceutical firms have large positive cash balances and are actually net lenders rather than net borrowers (i.e. they have a negative debt ratio). Incorporating this point into their CAPM analysis for January, 1990, causes the estimated nominal value of the cost of capital to increase by almost a full percentage point (see Myers and Shyam-Sunder, 1996, p. 223). In addition, as noted in footnote 4, many firms appear to use higher costs of capital in their R&D investment decisions than what emerges from this CAPM analysis.

Table 3
Average phase times and clinical period capitalized costs for investigational compounds (in millions of 2000 dollars)[a]

Testing phase	Mean phase length	Mean time to next phase	Capitalized mean phase cost[b,c]	Capitalized expected phase cost[b,c]
Phase I	21.6	12.3	30.5	30.5
Phase II	25.7	26.0	41.6	29.5
Phase III	30.5	33.8	119.2	37.4
Long-term animal	36.5	–	9.5	3.0
Total				100.4

[a] All costs were deflated using the GDP Implicit Price Deflator. Weighted values were used in calculating means, medians, and standard deviations for costs and phase times. Phase times are given in months.

[b] The NDA approval phase was estimated to be 18.2 months. Animal testing was estimated to begin 4.2 months after the initiation of phase I.

[c] Costs were capitalized at an 11% real discount rate.

98.9 months for the earlier study. The difference is accounted for by the much shorter FDA approval times in the mid to late 1990s that were associated with the implementation of the *Prescription Drug User Fee Act of 1992*. While the approval phase averaged 30.3 months for the earlier paper's study period, that phase averaged only 18.2 months for drugs covered by the current study.

Other things being equal, the observed shorter times from clinical testing to approval yield lower capitalized costs relative to out-of-pocket costs. However, the discount rate that we used for the current study is also higher than for the previous study (11% versus 9%). The two effects work in offsetting ways. On net, there was very little difference between the studies in the ratio of mean capitalized to out-of-pocket cost for the individual clinical phases.[25]

5.4. Clinical cost per approved new drug

Although average cost estimates for investigational drugs are interesting in their own right, we are mainly interested in developing estimates of cost per approved new drug. To do so, we need an overall clinical approval success rate. Our statistical analysis of compounds in the Tufts CSDD database of investigational drugs that met study criteria yielded a predicted final clinical success rate of 21.5%. Applying this success rate to our estimates of out-of-pocket and capitalized costs per investigational drug results in estimates of cost per approved new drug that link the cost of drug failures to the successes.

Aggregating across phases, we find that the out-of-pocket clinical period cost per approved new drug is US$ 282 million and the capitalized clinical period cost per approved new drug is US$ 467 million. These costs are more than four-fold higher than those we found in our previous study.

[25] The ratios of capitalized to out-of-pocket cost for the earlier study were 1.9, 1.7, 1.4, and 1.6 for phases I–III, and animal testing, respectively. For this study, we found the ratios to be 2.0, 1.8, 1.3, and 1.8 for phases I–III, and animal testing, respectively.

5.5. Preclinical out-of-pocket and capitalized costs per approved drug

The preclinical period, as defined here, includes discovery research as well as preclinical development. As noted above, not all costs during this period can be allocated to specific compounds. To deal with this issue, we analyzed aggregate annual firm expenditures on self-originated new drugs by the preclinical and clinical periods. We gathered data on aggregate expenditures for these periods from survey firms for 1980–1999. Both times series tended to increase over time in real terms. Given this outcome, and the fact that the clinical expenditures in 1 year will be associated with preclinical expenditures that occurred years earlier, the ratio of total preclinical expenditures to total R&D (preclinical plus clinical) expenditures over the study period will yield an overestimate of the share of total cost per new drug that is accounted for by the preclinical period. To accurately estimate this share we built in a lag structure that associates preclinical expenditures with clinical expenditures incurred some time later. Using data in the Tufts CSDD database of approved drugs, we estimated the average time from synthesis of a compound to initial human testing for self-originated drugs to be 52.0 months. Our analysis of clinical phase lengths and phase gaps and overlaps indicates a period of 68.8 months over which clinical period development costs are incurred. We approximate the lag between preclinical and clinical expenditures for a representative new drug as the time between the midpoints of each period. This yields a lag of 60.4 months, or approximately 5 years. Thus, we used a 5-year lag in analyzing the aggregate expenditure data. Doing so resulted in a preclinical to total R&D expenditure ratio of 30%. This share was applied to our clinical cost estimates to determine corresponding preclinical cost estimates. Given the estimates of out-of-pocket and capitalized clinical cost per approved new drug noted in Section 5.4, we can infer preclinical out-of-pocket and capitalized costs per approved new drug of US$ 121 and 335 million, respectively. The results are very robust to different values for the length of the lag structure. For example, if we assume a lag of 4 years instead of 5 years, then out-of-pocket preclinical costs would be 9.8% higher. Alternatively, if we assume a 6-year lag, then out-of-pocket preclinical costs would be 9.3% lower.

5.6. Total capitalized cost per approved drug

Our full cost estimate is the sum of our preclinical and clinical period cost estimates. Our base case out-of-pocket cost per approved new drug is US$ 403 million, while our fully capitalized total cost estimate is US$ 802 million. Time costs, thus, account for 50% of total cost. This share is nearly identical to one that we found in our previous study (51%). This is the case even though the time cost shares for both the clinical and preclinical periods are somewhat higher for this study. The explanation for this seeming inconsistency is that time costs are relatively greater for preclinical expenditures since they are incurred earlier in the process, but the preclinical share of total costs is lower for the present study.

5.7. Trends in R&D costs

Fig. 2 presents the primary results (capitalized preclinical, clinical, and total cost per approved new drug) for the previous two studies and for our current study. In inflation-adjusted

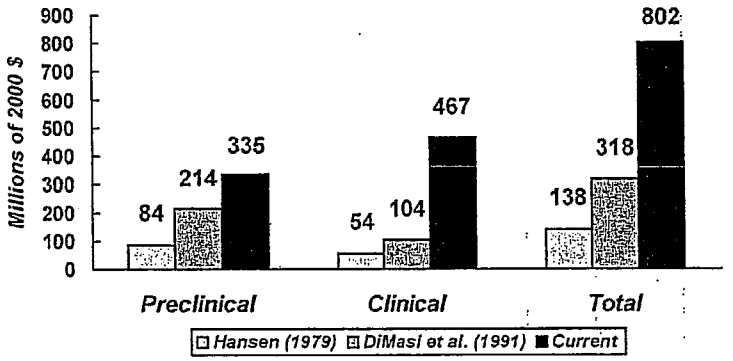

Fig. 2. Trends in capitalized preclinical, clinical and total cost per approved new drug.

terms, total capitalized cost was 2.3 times higher for the previous study in comparison to the first study. Real total capitalized cost per approved new drug for the current study is 2.5 times higher than for the previous study. However, the samples for these studies include drugs that entered clinical testing over periods that are not uniformly dispersed. In addition, while the samples were chosen on the basis of when drugs entered clinical testing, changes over time in the average length of the development process make ascribing differences in the study periods according to the year of first human testing problematic. An alternative is to determine an average approval date for drugs in each study's sample and use the differences in these dates to define the time differences between the studies. This will allow us to determine annual cost growth rates between successive studies.

Drugs in the current study sample obtained FDA marketing approval from 1990 to 2001, with the vast majority of the approvals occurring between 1992 and 2000. The mean and median approval date for drugs in the current study's sample was in early 1997. For the previous study, we reported that the average approval date was in early 1984. Thus, we used 13 years as the relevant time span between the studies and calculated compound annual rates of growth between the two studies accordingly.

Hansen (1979) did not report an average approval date; however, we can infer a period difference by noting the sample selection criteria and the difference in development times between that study and the DiMasi et al. (1991) study. The sample selection criteria for DiMasi et al. (1991) involved a 7-year shift in initial clinical testing relative to Hansen (1979). However, the estimated time from the start of clinical testing to marketing approval was 2.3 years longer for the DiMasi et al. (1991) study. Thus, we use 9.3 years as the difference between the study periods for these two studies.

Using these period differences, we found that the compound annual growth rates in total out-of-pocket cost per approved drug were quite similar across the studies (Table 4). The growth in total costs, however, masks substantial differences in growth rates for the preclinical and clinical periods. While out-of-pocket preclinical expenditures continued to grow in real terms, its growth rate for the current study relative to the previous one declined by two-thirds in comparison to the growth rate for the first two studies. Conversely, the growth rate for clinical period expenditures approximately doubled for the two most recent studies.

Table 4
Compound annual growth rates in out-of-pocket and capitalized inflation-adjusted costs per approved new drug[a]

Period	Out-of-pocket			Capitalized		
	Preclinical (%)	Clinical (%)	Total (%)	Preclinical (%)	Clinical (%)	Total (%)
1970–1980	7.8	6.1	7.0	10.6	7.3	9.4
1980–1990	2.3	11.8	7.6	3.5	12.2	7.4

[a] Costs for the 1970s approvals are from Hansen (1979), costs for the 1980s approvals are from DiMasi et al. (1991), and costs for the 1990s approvals are from the current study.

Annual growth rates for capitalized costs are also shown in Table 4. The results show a substantially higher growth rate for clinical costs for the two most recent analyses. However, while the growth rate for total out-of-pocket cost per approved drug was slightly greater for the two most recent studies, the growth rate in total capitalized cost was two percentage points higher between the first and second study than between the second and third. This is so, despite the fact that the discount rate increased one percentage point between the first two studies, but two percentage points between the last two. The growth rate in capitalized costs, however, is driven more by the fact that preclinical costs have a lower share of total out-of-pocket costs in the current study than in the previous studies, and time costs are necessarily proportionately more important for preclinical than for clinical expenditures.

6. Sensitivity analysis

6.1. *Effects of parameter changes*

We undertook sensitivity analyses for several of the key parameters that underlie the cost estimates. Fig. 3 shows how preclinical, clinical, and total capitalized costs would vary by discount rate at half-percentage point intervals. The values for a zero percent discount rate are out-of-pocket costs. In the neighborhood of our base case discount rate (11%), clinical cost changes by about US$ 10 million, preclinical cost changes by about US$ 15 million,

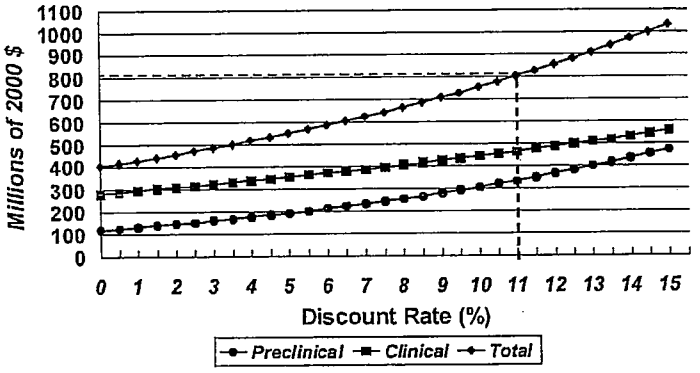

Fig. 3. Capitalized preclinical, clinical, and total costs per approved new drug by discount rate.

and total cost changes by about US$ 25 million for every half of one percent shift in the discount rate. In our previous study, the base case discount rate was 9%. At a 9% discount rate, total capitalized cost here is US$ 707 million, or 11.8% less than our base case result. The results in section 5.3 provide some support for an even higher discount rate than our base case value. At a 12% discount rate, total capitalized cost per approved new drug is US$ 855 million, or 6.6% higher than our base case result.

The clinical approval success rate is another key parameter. We analyzed the effects of an approximate 10% change in the success rate at various discount rates. A higher success rate has a somewhat smaller impact on total cost than does a correspondingly lower success rate. At our base case discount rate, total capitalized cost for a success rate of 23.5% is US$ 734 million, or 8.5% lower than our base case result. At a success rate of 19.5%, total capitalized cost is US$ 885 million, or 10.3% higher than our base case result. The estimated clinical success rate for our previous study was 23.0%. At that success rate, total capitalized cost here is US$ 750 million, or 6.5% less than our base case result.[26]

The methodology for determining the total capitalized cost estimate is dependent on values for 20 parameters. However, not all of them are independent of one another. It is possible to determine total capitalized cost from estimates of 16 parameters. To get a measure of statistical error for overall cost, we performed a Monte Carlo simulation (1000 trials) for total capitalized cost by taking random draws from the sampling distributions of the 16 parameters and computing a total cost estimate for each simulation trial.[27] Ninety-five percent of the total cost estimates for the simulation fell between US$ 684 and 936 million, 90% fell between US$ 705 and 917 million, and 80% fell between US$ 717 and 903 million.[28] The interquartile range was US$ 757–854 million.

[26] These analyses indicate what the results would be if the clinical success rate is changed, while other parameters remain the same. If the phase attrition rates are adjusted to be consistent with the new clinical success rate while maintaining the same distribution of failures across phases, then the differences in cost are somewhat lower. For example, if the clinical success rate is 23.0% and phase attrition rates are altered accordingly, total capitalized cost is 5.6% lower (5.1% lower if account is also taken of estimated differences in phase costs between the failures and successes in the sample [see the following section]).

[27] The clinical success rate parameter is determined from the values of four asymptotically normal coefficient estimates. We performed an initial Monte Carlo simulation for the clinical success rate using these coefficient estimates and their standard errors to obtain a sampling distribution for the success rate. The sampling distribution for the discount rate was chosen by assumption. Given that the base case choice of discount rate may be somewhat conservative (see the discussion above), we chose a triangular distribution for the discount rate that varied from 10.0 to 12.5%, with the modal value for the distribution chosen so that the mean discount rate is approximately 11.0% in the simulations for total capitalized cost. The other sampling distributions were for estimated means and binomial probabilities. Finite population correction factors were applied to the standard errors.

[28] The simulation was conducted assuming statistical independence for the parameters. The out-of- pocket phase cost, development time, and success and attrition rate parameters were estimated from separate datasets, and so their independence of one another is likely. It is possible that out-of- pocket phase costs are correlated. We therefore also conducted a simulation using the estimated correlations across phases for those pairs that were found to have correlations that were statistically significantly different from zero (phases I and II [0.496], phases II and III [0.430], phase II and long-term animal testing [0.656]). This increased the variability of the total capitalized cost estimates only slightly. Specifically, the coefficient of variation increased from 0.088 to 0.099. The main simulation results were affected most by variability in individual phase costs, and least by variability in development times. The coefficient of variation when only development times vary, when only the discount rate varies, when only success and attrition rates vary, and when only out-of-pocket phase costs vary were 0.015, 0.035, 0.044, and 0.065, respectively.

6.2. Variable discount rates

Myers and others (Myers and Shyam-Sunder, 1996; Myers and Howe, 1997) have argued that the cost-of-capital for R&D should decline over the development process as a step function. They termed the relationship a risk-return staircase. In the case of pharmaceutical R&D, the staircase is not related to the usual notions of risk in pharmaceutical development (i.e. the probabilities of approval at different points in the process). These technical risks can be diversified away by investors, who can spread their investments over many firms. Rather, the rationale has to do with the notion that at any point in the development process future R&D costs serve as a kind of leverage, or debt, if the firm wishes to proceed with development and market a product. A more levered position amplifies risk and is associated with a higher cost-of-capital for investors. Since the leveraging declines over the development process, so does the cost-of-capital. Technical risks play a role only in that they affect expected future costs.

The valuation problem may also be viewed as a compound option pricing problem. The firm effectively faces call options at decision points during development, where the exercise price is the cost of future R&D. Myers and Howe (1997) suggest a means for dealing with the problem that reduces the informational requirements to knowledge of two-discount rates. One of these is the discount rate for net revenues on a marketed drug (r_{NR}). The other is the discount rate on future costs (r_{FC}). The rate for net revenues should be somewhat less than the overall company COC. The rate for future costs, being an expected return on what is nearly a fixed debt obligation, is likely lower. Under certain assumptions, the Myers and Howe (1997) two-discount rate method yields the same results as the more complex compound options valuation. We view this approach to discounting as experimental for our purposes. To our knowledge, no pharmaceutical firm uses such an approach for its project evaluations. In addition, although they may be guided by real world information, the selections of the two-discount rates are judgment calls.[29]

For purposes of comparison, we did compute drug R&D costs with the Myers and Howe (1997) two-discount rate method. Their base case values for r_{NR} (9%) and r_{FC} (6%) were meant to be relevant for 1994, which corresponds roughly with the middle of our study period. Thus, we computed the total capitalized pre-approval cost per approved drug using these values and other close combinations in a sensitivity analysis. At the Myers and Howe (1997) base case values, total capitalized cost is marginally higher than our estimate computed at an 11% COC (US$ 815 million). However, the total capitalized cost estimate is US$ 955 million when a 10% discount rate is used for r_{NR} and a 5% discount rate is used for r_{FC}. Conversely, at an 8% discount rate for r_{NR} and a 7% discount rate for r_{FC}, the total cost estimate is US$ 696 million.

[29] For their financial life-cycle simulation model, Myers and Howe (1997) chose base case values for r_{NR} and r_{FC} partly on the basis of judgment and partly because these values generated realistic company costs-of-capital for mature pharmaceutical firms in their simulations. These simulations required assumptions about revenue distributions and other factors that affect profitability.

7. Extensions to the base case

The base case results on overall pre-approval drug development costs can be extended in several interesting ways. Our base case results link the costs of the failures to the successes. We can provide estimates of the clinical period cost of taking a successful drug all the way to approval by examining the data for the approved drugs in the sample. This also allows us to obtain some evidence on costs for the more medically significant products (according to what is known at the time of approval) by using an FDA prioritization ranking for approved drugs. We can also use data collected from our survey to estimate R&D expenditures on new drugs subsequent to original marketing approval. Finally, we can examine what impact tax policies and procedures have had on the effective cost of pharmaceutical R&D for pharmaceutical firms.

7.1. Development costs for successes

As our results indicate, development costs vary across drugs. Thus, it is worthwhile to examine specific subclasses of drugs, where one may reasonably conjecture that the cost structure is different than it is for drugs as a whole. In particular, we investigated the clinical cost structure for successful drugs (i.e. drugs that have made it through testing and obtained marketing approval from the FDA). We also examined these data classified by an FDA rating of therapeutic significance for drug approvals.

Of the 68 drugs in our sample, 27 have been approved for marketing. We had complete phase cost data for 24 of the approvals. Clinical phase cost averages and standard deviations for the approved drugs in the sample are shown in Table 5. For comparative purposes, the results for the full sample are also shown. Except for phase I, clinical phase costs are notably higher for the approved drugs than for drugs as a whole. Phase II and III costs for the approved drugs are 77 and 18% higher, respectively. This result is qualitatively consistent with what we found in our previous study. An explanation that we offered therein may still be appropriate. The results may reflect a tendency to prioritize development by directing more resources, possibly by conducting more studies concurrently, to investigational drugs that appear, after early testing, to be the most likely to be approved. Since we are not linking

Table 5
Out-of-pocket clinical period phase costs for approved compounds (in millions of 2000 dollars)[a]

Testing phase	Approved drugs[b]			Full sample[c]		
	Mean cost	Median cost	Standard deviation	Mean cost	Median cost	Standard deviation
Phase I	15.2	11.7	14.3	15.2	13.9	12.8
Phase II	41.7	31.5	30.2	23.5	17.0	22.1
Phase III	115.2	78.7	95.0	86.3	62.0	60.6
Long-term animal	4.4	0	5.4	5.2	3.1	4.8

[a] All costs were deflated using the GDP Implicit Price Deflator.
[b] Estimates for the approved drugs are based on data for 24 of the 68 sample drugs.
[c] Weighted values were used in calculating means, medians, and standard deviations for the full sample.

failures to successes here and since we have full phase cost data for the 24 approved drugs, we can add phase costs for each drug to determine a total clinical period cost for each drug and use those data to find confidence intervals for mean out-of-pocket and capitalized clinical period cost for approved drugs. Mean out-of-pocket clinical period cost for the approved drugs was US$ 176.5 million, with a 95% confidence interval of US$ 126–227 million. We used actual phase timing for individual approved drugs, rather than averages over all approved drugs, to capitalize costs for individual approved drugs. Doing so yielded a mean clinical period capitalized cost of US$ 251.3 million, with a 95% confidence interval of US$ 180.2–322.4 million.

The FDA prioritizes new drugs by therapeutic significance at the time of submission of an application for marketing approval.[30] New drugs are rated as either priority (P) or standard (S).[31] Kaitin and Healy (2000), Kaitin and DiMasi (2000), Reichert (2000), and DiMasi (2001a) contain numerous analyses of development and approval times by FDA therapeutic rating. However, the only prior analysis of development costs by therapeutic rating was in our previous study. We found higher mean clinical phase costs for more highly rated drugs. The results for this sample also show higher costs. Mean clinical period out-of-pocket cost for approved drugs with a P rating was US$ 207 million, compared to US$ 155 million for drugs that had received the S rating.

The differential was less for capitalized costs. Mean clinical period capitalized cost was US$ 273 million for drugs with a P rating and US$ 236 million for those with the S rating. In both cases, the confidence intervals for P and S rated drugs overlap. However, given the substantial variability in drug development costs and the fact that the number of compounds in each category was small (10 drugs with a P rating and 14 with an S rating), this outcome is not surprising. However, it is plausible that, on average, testing a priority-rated drug breaks more new scientific ground and so is costlier, as firms must learn through experience. It may also be the case that firms have the incentive to do more wide-ranging and costly testing on drugs that have the potential to be both clinically and commercially significant. Our results can then be viewed as supportive, but not conclusive, evidence of higher costs for drugs with higher therapeutic significance ratings.

7.2. *Cost of post-approval R&D*

Our main objective was to estimate pre-approval R&D costs. However, our pre-approval estimates together with other pharmaceutical industry data regarding the drug development process allowed us to construct an estimate of the cost of post-approval R&D, and thereby obtain an estimate of average total R&D cost per new drug covering the entire

[30] The process is intended to provide direction for internal prioritization of marketing approval reviews by the FDA. The *Prescription Drug User Fee Act of 1992* and its reauthorization in 1997 include performance goals for the FDA that are defined in terms of the therapeutic ratings.

[31] In late 1992 the FDA switched from a three-tiered rating system (A, B, C) to the current two-tiered system (P, S). Drugs that were rated A were judged to represent a significant gain over existing therapy, those rated B were judged to represent a moderate gain over existing therapy, and those rated C were judged to represent little or no gain over existing therapy. Our sample includes drugs that were rated under the old system. We assigned drugs that had received an A or B rating to the P category, and drugs that had received a C rating to the S category under the current system.

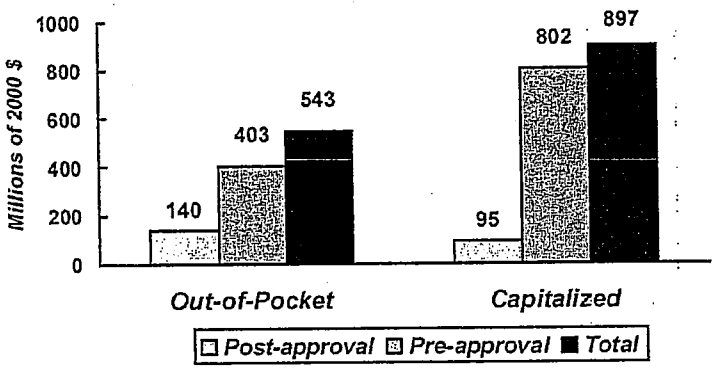

Fig. 4. Out-of-pocket and capitalized total cost per approved new drug for new drugs and for improvements to existing drugs.

development and marketing life-cycle. The aggregate annual expenditure data that we collected for the cost survey firms show that these firms spent approximately three-quarters of their prescription pharmaceutical R&D expenditures on self-originated new drugs, 10% on investigational drugs that are licensed-in or otherwise acquired, and 15% on improvements to drugs that have already been approved.

We cannot, however, use the percentage of aggregate R&D expenditures spent on post-approval R&D on a current basis and apply it to our pre-approval cost estimate to obtain an estimate of the cost of post-approval R&D per approved drug. The reason is that pre-approval costs occur years before post-approval costs. We may use our aggregate annual firm R&D data, but we must build in a reasonable lag structure. Our methodology for doing so is discussed in detail in an appendix that is available from the authors upon request (Appendix A).

We used a 10-year lag for the aggregate data (approximate time between median pre-approval development costs and median post-approval costs), assumed that post-approval R&D cost per approval is the same, on average, for licensed-in and self-originated drugs, and determined the percentage of approvals for the cost survey firms that are self-originated to estimate the ratio of post-approval R&D cost per approved drug to pre-approval cost per approved drug. The data indicated that this share was 34.8%. Thus, we estimated the out-of-pocket cost per approved drug for post-approval R&D to be US$ 140 million (Fig. 4). Since these costs occur after approval and we are capitalizing costs to the point of marketing approval, our discounted cost estimate is lower (US$ 95 million). Thus, out-of-pocket cost per approved drug for post-approval R&D is 25.8% of total R&D cost (pre- and post-approval), while capitalized cost for post-approval R&D is 10.6% of total cost.

7.3. *Tax analysis*

The cost estimates that are presented here are pre-tax. As noted above, OTA (1993) used the basic data and methodology from our previous study in their report, but the OTA also reported an after-tax figure determined by subtracting a percentage of pre-tax capitalized cost. The percentage was an assumed average effective corporate income tax rate for the

period. Hence, a straightforward calculation can be made to use our R&D cost estimates as inputs in after-tax analyses of R&D rates of return (OTA, 1993; Grabowski and Vernon, 1994). However, some have suggested that an after-income tax figure is the relevant measure of pharmaceutical industry R&D cost (Public Citizen, 2001).

As a stand-alone estimate for R&D cost, we find such a figure to be inadequate for our purposes and potentially misleading. First, we are primarily interested in trends in private sector resource costs associated with getting a new drug to regulatory marketing approval. Tax rates and tax structures can change over time, so trends in resource costs can be masked by after-tax figures. Second, even if the objective is to measure the effective cost to companies, that cost is not properly measured by subtracting the corporate income tax deduction for R&D from the resource cost estimate. It can also be misleading, as it may suggest that government is subsidizing corporate R&D by the amount of the deduction. The corporate income tax is intended to be a tax on profits. Deductions for R&D and other business costs are the means used to approximate the appropriate base for the tax (revenues minus costs). Thus, cost deductions on corporate income tax statements cannot be properly viewed as tax breaks.

The only potential tax advantage with respect to administration of the corporate income tax involves the timing of tax payments. R&D is an investment, but firms are allowed to deduct R&D costs (excluding plant and equipment) as current expenses in lieu of depreciating these investment costs over time. Nevertheless, the value of this timing effect should be significantly less than the total deduction.[32] The accounting informational requirements needed to appropriately depreciate an intangible asset such as R&D are so formidable that expensing of R&D is allowed under accounting guidelines. The true economic depreciation schedule likely varies significantly by industry, by firms within an industry, and by project within a firm. Thus, the practice of allowing what is in effect a 100% depreciation rate in the first year can be viewed as a second-best solution for an otherwise intractable issue.

A portion of the US tax code that is intended to serve as a stimulus to innovation by effectively subsidizing R&D is the Research and Experimentation (R&E) tax credit. The R&E tax credit was not relevant to a significant degree to the study period for our previous analysis (DiMasi et al., 1991). However, it is almost fully applicable to the study period for the current analysis. The credit is generally determined as a percentage of the *excess* of qualified R&D expenditures in a year over a base amount. It is difficult to adequately assess the quantitative impact of this tax policy. Over the history of the implementation of the R&E tax credit, the percentage credited has changed, as has the method for determining

[32] In theory, optimal administration of the tax would involve depreciating all forms of intangible capital at economically appropriate rates. However, tax savings relative to the theoretical optimum should be measured in a tax revenue-neutral context. If intangible capital were depreciated rather than expensed, then the present value of tax revenues would increase. To keep revenues constant, the tax rate would have to be lowered. If all industries were identical with respect to the degrees to which they utilized intangible capital of all types, then tax burdens would not be any different in the alternative state (abstracting from any induced secondary effects on the distribution of industry allocations between tangible and intangible capital or between labor and capital). The pharmaceutical industry, however, is almost certainly above-average in terms of investment in intangible capital (Clarkson, 1977). If the optimal state is attainable at reasonable cost, the tax savings to the pharmaceutical industry, then, is not the difference in the present values of its tax burden as between the current state and the optimum at the current tax rate, but something less that depends on the extent to which the pharmaceutical industry is above-average with regard to investment in intangible capital.

the base amount.[33] It seems unlikely, though, that the credit has had a substantial economic impact on large multinational pharmaceutical firms.[34]

Since 1983 an orphan drug tax credit has also been available to manufacturers for clinical trial expenses related to the development of drugs for orphan indications (fewer than 200,000 patients afflicted in the United States or where it can be demonstrated that development is not profitable). However, for a number of reasons the empirical significance of this credit for the type of firm surveyed for this study is likely to be very small.[35] Analysis of data provided in a Congressional Research Service (CRS) report indicates that orphan drug tax credits amount to a fraction of a percent of pharmaceutical industry R&D expenditures (Guenther, 1999).[36]

[33] In the early implementation years the credit percentage was 25%, but that was lowered to 20% in 1987. The base amount had been an average of research expenditures that met certain criteria for the three previous tax years. In most instances it now essentially involves applying an historical R&D-sales ratio (any 5 years from 1983 to 1988) to the average of gross receipts for the previous 4 tax years. The credit can be applied only to the excess of current "qualified research expenses" over the base amount. A variety of R&D expenditures are excluded from consideration. For example, management expenses other than first-line supervision of those directly engaged in research activity, some computer software development costs, and 35% of research expenses contracted out to for-profit firms are not counted. The credit also does not apply to research conducted outside the United States, Puerto Rico, or any possession of the United States. In addition, firms will typically elect to reduce the allowed credit by the maximum corporate income tax rate (currently 35%). If they do not, then they must reduce the research expenses that they deducted on their corporate income tax statements by the amount of the credit.

[34] Many firms do not separately report R&E tax credits in their published financial data. We did find R&E credits reported in the public financial statements of seven large pharmaceutical firms for each year from 1999 to 2001 (GlaxoSmithKline, Johnson & Johnson, Lilly, Pfizer, Pharmacia, Schering-Plough, and Takeda) and for 2001 for American Home Products (now Wyeth). We compared the credit amounts to the firms' reported R&D expenses. R&E credits as a percentage of R&D expenditures varied somewhat by firm and year (0–5.2%). Overall, the tax credits amounted to 2.0% of R&D expenditures. Adding Merck, which reported on a broader category (General Business Credits), increased the share only to 2.1%. One might argue that prescription pharmaceutical R&D could contribute more to the accumulation of R&E tax credits than is indicated by these data. This might be so if prescription pharmaceutical R&D expenditures grow more rapidly than the firms' other R&D expenditures (this effect would be mitigated, though, in the long-run if pharmaceutical sales also increase at a rate that is greater than for the firms' other businesses). We do not know if this has been the case. However, even if it has, that impact could be more than reversed if firms have made greater use of outsourcing in pharmaceutical than in non-pharmaceutical R&D. By all accounts, pharmaceutical firms have contracted out drug development activities at a rapidly growing rate over our study period, and the share of pharmaceutical R&D expenditures currently accounted for by outsourcing is substantial. As noted above, a significant share of outsourced R&D is excluded from the tax credit calculations.

[35] Unless it can be demonstrated that it is necessary to go outside the United States to find patients, the credit (50% of qualified clinical trial expenses) is not available for foreign trial costs. It is also cannot be applied to clinical testing on any non-orphan indications for a compound with an orphan drug designation. In addition, the vast majority of the manufacturers with products that have received orphan drug designations are biotech firms or small niche pharmaceutical firms (see http://www.fda.gov/orphan/designat/list.htm). For development as a whole, it is highly likely therefore that the share of R&D expenditures for which the orphan drug credit was applicable for traditional large multinational pharmaceutical firms is quite low.

[36] The report includes data on both orphan drug tax credits and taxable income for the pharmaceutical industry for 1990–1994. The CRS also noted in its report that 20.3% of US pharmaceutical industry domestic sales and exports were spent on R&D in 1997. Applying this R&D-sales ratio to the data on taxable income suggests that orphan drug credits amounted to 0.3% of R&D expenditures. This is a conservative estimate for large pharmaceutical firms since taxable income is determined by deducting business expenses from sales, and since, as noted above, biotechnology and small pharmaceutical firms obtain a disproportionate share of the credits.

8. Validation

In their 1993 report, the OTA reviewed the literature on pharmaceutical R&D costs. In addition to critiquing the methodologies used in these studies, the review addressed evidence on the reasonableness of the studies, particularly the DiMasi et al. (1991) study. The OTA concluded that, "the estimates by DiMasi and colleagues of the cash outlays required to bring a new drug to market and the time profile of those costs provide a reasonably accurate picture of the mean R&D cash outlays for NCEs first tested in humans between 1970 and 1982" (OTA, 1993, p. 66). The OTA provided varied data and analyses to corroborate the results in DiMasi et al. (1991). We corroborate the basic cost results in this study by examining the representativeness of our sample firms and by analyzing various independently derived results and data about the industry and the drug development process. We pay particular attention to data that corroborate the growth in costs between the previous study and the current one.

8.1. Internal validation

The Tufts CSDD database of investigational compounds, from which our sample was selected, contains data on the vast majority of new drugs developed in the United States (DiMasi, 2001a). The distribution of investigational drugs across therapeutic classes for our 10 survey firms is very close to the distribution for all drugs in the database. We examined the data for eight specific therapeutic classes and one miscellaneous class for drugs in the database that met study inclusion criteria. There are 530 compounds in the database that meet these criteria and for which a therapeutic class could be identified (272 of these compounds belong to the 10 cost survey firms). The largest difference in share for a specific class between all firms in the database and the cost survey firms was 1.5%.[37] Using a chi-squared goodness-of-fit test comparing the therapeutic class distributions for the cost survey firms and the other firms in the database, we found no statistically significant difference for the class shares ($\chi^2 = 5.01$, d.f. $= 9$).[38]

Based on publicly available data, we also found that pharmaceutical R&D expenditure growth rates for the survey firms as a whole were similar to the reported growth rates for all PhRMA member firms. For example, the annual growth rate in real pharmaceutical R&D expenditures for the survey firms[39] from 1995 to 2000 is 11.3%, compared to 11.0% for PhRMA member firms over the same period.[40]

[37] The population shares for the analgesic/anesthetic, antiinfective, antineoplastic, cardiovascular, central nervous system, endocrine, gastrointestinal, immunologic, miscellaneous, and respiratory classes are 9.1, 12.8, 9.4, 23.2, 17.9, 7.0, 2.1, 3.0, 9.4, and 6.0%, respectively. The corresponding shares for the cost survey firms are 9.6, 14.3, 8.1, 22.8, 19.1, 7.4, 2.2, 3.3, 7.7, and 5.5%, respectively.

[38] The estimated clinical success rate for all firms in this dataset (21.5%) is also very close to the estimated success rate for the 10 firms using the same inclusion criteria (22.2%).

[39] The data are for nine of the 10 firms. We did not find pharmaceutical R&D data for one of the firms, but this firm has a relatively small pharmaceutical subsidiary whose inclusion would not materially affect the results. The data were taken from Scrip's Pharmaceutical Company League Tables (various years) and company annual reports.

[40] The annual growth rate for 1995–1999 was slightly lower for the survey firms compared to all PhRMA member firms (11.5% versus 11.8%).

8.2. External validation

Publicly available data that were collected independently can be examined to determine the extent to which they are consistent with our results in terms of levels or rates of change. Specifically, we examined independent information on clinical trial sizes, measures of clinical trial complexity, and published trade association data on R&D employment and expenditures.

8.2.1. Clinical trial sizes and complexity

Several groups have compiled data on clinical trial sizes for new molecular entities approved in the United States for periods that range from the late 1970s to 2001 (BCG, 1993; OTA, 1993; Peck, 1997; PAREXEL, 2002).[41] Averaging the BCG results for 1981–1984 and 1985–1988 (2277) and comparing them to average of the Peck (1997) and PAREXEL (2002) results for 1994–1995 and 1998–2001 (5603) yields an annual growth rate in clinical trial sizes of 7.47% per year.[42] We may approximate the increases in cost per subject over time by examining the excess of medical care inflation over general price inflation. The medical care component of the CPI increased at an average annual rate of 6.73% from 1984 to 1997, while general price inflation (applying the price index used to deflate costs for this study) rose at an annual rate of 3.06% over the same period. Thus, other things being equal, these results suggest an increase of 11.4% per year in clinical trial costs. This compares to our finding of an 11.8% annual growth rate in out-of-pocket clinical period cost between DiMasi et al. (1991) and the current study.

These separate estimations need not be in perfect agreement because our clinical cost figures include costs not directly related to the number of clinical trial subjects (infrastructure costs, fixed costs related to production of clinical trial supplies, animal testing during the clinical period, etc.). In addition, there could be some economies of scale in clinical testing that would result in a somewhat lower growth in cost per subject. However, data compiled by DataEdge, LLC (PAREXEL, 2002, p. 96) indicate that the complexity of clinical trials

[41] Each of these sources obtained data for a sample of the US approvals during specific periods. The BCG found the mean number of subjects included in NDAs to be 1576 for 1977–1980, 1321 for 1981–1984, and 3233 for 1985–1988. OTA (1993) compared clinical trial sizes for NDAs for three therapeutic categories (antihypertensives, antimicrobials, and nonsteroidal antiinflammatories) over two periods. In aggregate, it found the mean number of subjects to be 2019 for 1978–1983 approvals ($n = 28$) and 3128 for 1986–1990 approvals ($n = 25$). Peck (1997) found the mean number of subjects to be 5507 for 12 of 50 1994–1995 approvals. PAREXEL (2002) has examined the number of subjects in NDAs for 55% of the new molecular entities approved by the FDA in each year from 1998 to 2001. For the period as whole, the mean number of subjects is 5621 ($n = 64$). The latter two averages are similar to what we have found as the mean number of subjects across all three clinical phases for the investigational drugs in our cost survey (5303). CMR (2000) found the mean number of subjects to be 4478 for 23 marketing approval applications submitted from 1995 to 2000. However, only nine of the submissions were to the FDA, with the remainder submitted to European Union and Japanese regulatory authorities. Since pre-approval costs are measured here up to the point of US regulatory approval, we use the US-based data.

[42] These groupings were chosen so that the mean approval years were 1984 and 1997 (the average approval years for the DiMasi et al. (1991) and the current cost samples). The difference in the two periods was taken to be 12.5 years. For the early period, we prefer the BCG data to the OTA data, since the OTA data apply to only three therapeutic categories that likely tend, in aggregate, to have above-average clinical trial sizes.

has increased significantly in recent years. Their index of clinical trial complexity[43] for phases I–III increased at an annual rate of 4.8% per year from 1992 to 2000. An increase in clinical trial complexity will contribute to even higher growth rates for clinical costs.[44]

8.2.2. Growth in industry R&D employment costs

Despite rapid growth in outsourcing of R&D activities over the last few decades, pharmaceutical firms have significantly expanded the number of their own employees devoted to the R&D function. In its industry profile and annual survey reports over various years, PhRMA has provided annual information on the R&D employment of its member firms. From 1980 to 2000, total R&D employment increased at a compound annual rate of 5.4%, with scientific and professional staff increasing at a 7.4% annual rate.[45]

We adjusted National Science Foundation (NSF) data on median annual salaries for full-time employed biological scientists with doctorates working in for-profit life sciences industries from 1993 to 1999 for inflation (GDP Implicit Price Deflator).[46] Real salaries increased at a rate of 1.75% per year over this period. The OTA presented similar data for every 2 years from 1973 to 1989 (OTA, 1993; pp. 62–63). The real growth rate in median annual salaries for biological scientists with doctorates employed in business or industry from 1981 to 1989 was 1.77%. Applying a real growth rate of 1.76% per year for compensation to a growth rate of 7.4% per year in employment yields a growth rate of 9.3% per year for labor costs. This is moderately higher than the growth rate of 7.6% per year that we found for total out-of-pocket cost per approved drug between our previous study and the current one.[47] Thus, some labor costs have grown fairly rapidly. Most of the growth in labor costs, though, has been due to increasing the labor force devoted to R&D, rather than to increases in real wages.

[43] The index is based on the mean number of medical procedures to be applied to patients in clinical trial protocols. Some of these procedures will be covered by insurance, but the index should provide at least a rough indicator of the degree to which the clinical trial process is increasing in complexity.

[44] DataEdge has also compiled information on certain clinical trial costs (investigator fees and central laboratory costs). Changes in cost due to increases in clinical trial complexity will be at least partially reflected in these data. PAREXEL (2002) reports their index of mean costs per subject across all clinical phases (I–IV) for each year from 1996 to 2000. The index increased at an average annual real rate of 5.33% over this period. Combining this growth rate with the above growth rate for clinical trial sizes suggests a 13.1% average annual real rate of increase in clinical trial costs. Piecing together the index values for years reported in earlier editions of PAREXEL (2002) yields a 3.54% real growth rate for 1993–2000. This would imply an 11.2% average annual real growth rate in clinical trial costs.

[45] Over our study period, highly trained personnel have comprised an increasingly large component of the pharmaceutical industry in-house R&D labor force. The share of total R&D personnel for the scientific and professional category in the PhRMA data increased from 56.3% in 1980 to 81.8% in 2000.

[46] The data were compiled for 1993, 1995, 1997, and 1999 by the NSF through surveys of doctoral scientists and engineers in the United States (National Science Foundation, various years). The NSF used a new survey instrument for 1993 and later. Data for every 2 years from 1973 to 1989 used somewhat different occupational definitions. Thus, these data may not be strictly comparable to the data for 1993 and beyond. Data were not available for 1991.

[47] The NSF survey data for 1993–1999 show a real increase of 1.2% per year in median annual salaries across all degrees for biological scientists working in the for-profit life sciences industries. Applying this growth rate to the growth rate of 5.4% for all pharmaceutical industry R&D personnel yields an increase of 6.7% per year in labor costs.

8.2.3. Cost estimates from published industry R&D expenditures

PhRMA has gathered information on aggregate industry R&D spending for decades. The resultant R&D expenditure time series can be linked to data on new drug approvals to develop rough estimates of out-of-pocket pharmaceutical R&D costs. As noted above, linking current expenditures to current approvals is an inadequate approach. Our estimated time profile for a representative drug and the pattern of costs over that timeline determined for this study can be used to construct a lag structure for aggregate expenditures and approvals.[48]

There are two complications regarding the PhRMA data that must be addressed before we can validate our estimates. One is that while PhRMA has traditionally disaggregated its reported R&D expenditure data into expenditures on new drugs and expenditures on improvements to existing drugs, it has not gathered information on how expenditures on new drugs can be further decomposed into expenditures on self-originated and on licensed-in new drugs. Our R&D cost estimates are for self-originated drugs, and a substantial portion of the R&D expenditures on licensed-in drugs are likely missing from the PhRMA data.[49] Thus, we need to associate lagged industry expenditures on self-originated new drugs with self-originated new drug approvals. The second complication is that, with the exception of 1 year, PhRMA has gathered information on the domestic expenditures of all its firms, but the foreign expenditures of only its US-owned members. Our method for dealing with these complications is described in detail in an appendix available from the authors upon request (Appendix B).

We related estimated lagged PhRMA member firm R&D expenditures on self-originated new drugs from 1978 to 1998 to the number of self-originated new drug approvals by PhRMA member firms from 1990 to 2000. The lag structure follows the phase time-expenditure profile implied by our data, with weights attached to aggregate expenditures over a 2–12 year period. The ratio of total lagged self-originated R&D expenditures to the total number of self-originated approvals yields an estimate of the out-of-pocket cost of new drug

[48] PhRMA also publishes a breakdown of annual R&D expenditures of its member firms by function (PhRMA, 2001). The share for the category "Clinical Evaluation: Phases I–III" in 1999 is 29.1%. This share cannot be compared to the clinical period share of total out-of-pocket cost per approved drug implied by our estimates for at least three reasons. First, clinical period costs in a given year are linked to pre-human R&D expenditures in past years, and the pharmaceutical R&D expenditure series shows substantial growth. Thus, shares based on current year expenditures will significantly understate the clinical portion. Second, portions or all of some categories are for expenditures on post-approval R&D and should be deducted from the base before a pre-approval clinical share is computed. For example, given their definitions, the categories for "Clinical Evaluation: Phase IV (11.7%)" and "Process Development for Manufacturing and Quality Control (8.3%)" would likely have to be taken entirely out of the base. In addition, portions of other categories also likely are associated with post-approval R&D. Third, our notion of clinical period costs extends beyond direct patient costs and includes fixed infrastructure costs and other costs incurred during the clinical period. The categories "Toxicology and Safety Testing (4.5%)," Pharmaceutical Dosage Formulation and Stability Testing (7.3%)," "Regulatory: IND and NDA (4.1%)," "Bioavailability (1.8%)," and "Other (9.0%)" would each have to be decomposed into shares for pre-human R&D, pre-approval clinical period R&D, and post-approval R&D. With a reasonable pre-human/clinical lag structure, it is possible to choose an allocation of the three periods for these functional categories that results in a clinical period share of pre-approval R&D expenditures that equals our estimated cost share. However, we are not aware of any data that allows one to make these allocations credibly. Thus, we concluded that the PhRMA data on functional categories could not be used as an external check on our results.

[49] The PhRMA data apply to member firms. Not every pharmaceutical firm (particularly foreign firms) and few biotechnology firms are members of the organization.

development.[50] We calculated a range for this ratio by using reported domestic industry R&D expenditures for a lower bound and domestic plus foreign (inclusive of estimates for foreign-owned firms) industry R&D expenditures as an upper bound. The result is a range of US$ 354–558 million for out-of-pocket cost per approved new drug (inclusive of failures). Our out-of-pocket cost estimate of US$ 403 million per approved drug calculated from our survey data falls within this range. Capitalizing the aggregate expenditure data using our phase-expenditure time profile yields a range of US$ 650–1023 million, which encompasses our total capitalized cost estimate of US$ 802 million.

We also conducted a check similar to what the OTA had done in its report (OTA, 1993, pp. 61–62). In theory, under our average development and approval time profile described above, all industry self-originated new drug R&D expenditures in 1988 would be associated with new drug approvals from 1990 to 2000. If each self-originated new drug approval from 1990 to 2000 by a PhRMA member firm is assumed to cost US$ 403 million, then we can use the yearly time-expenditure weights noted above to estimate PhRMA member firm total self-originated R&D expenditures in 1988. Doing so yields US$ 6176 million in 2000 dollars. This value fits within our range for self-originated new drug R&D expenditures estimated from the PhRMA data (US$ 4942–7777 million in 2000 dollars).

9. Conclusions

The cost of developing new drugs is a topic that has long engendered considerable interest. The interest has intensified recently as firms have become increasingly concerned about improving productivity in a period of consolidation and cost containment pressures in the marketplace, and industry critics question industry statements about the level of R&D costs and the impact that price regulation would have on R&D (Public Citizen, 2001).[51] We have undertaken the only comprehensive project-based analysis of the costs of drug development since our previous study (DiMasi et al., 1991). In the last study we estimated average R&D cost to be US$ 231 million in 1987 dollars. For our updated analysis, we estimated that total R&D cost per new drug is US$ 802 million in 2000 dollars. Our results were validated in an number of ways through analyses of independently derived published data on the pharmaceutical industry. Including an estimate of the cost per approved new drug for R&D conducted after approval increases total R&D cost to nearly US$ 900 million. Our pre-approval estimate represents a two and one-half-fold increase in real capitalized costs. On an annualized basis, the growth rate in inflation-adjusted cost was 7.6% for out-of-pocket expenditures and 7.4% for capitalized costs.

Roughly speaking, the current study covers R&D costs that yielded approvals, for the most part, during the 1990s. The previous study (DiMasi et al., 1991) generally involved

[50] We believe that aggregating over the expenditure and approval periods is superior to using an average of yearly ratios. Year-to-year ratios are highly variable since they are very sensitive to the denominator value (number of self-originated new drug approvals) for the year.

[51] Pre-approval R&D expenditures are sunk costs at the time a pricing decision has to be made. Thus, they should not affect price setting in an unregulated market. However, to the extent that high past R&D costs predict high future R&D costs, then anticipated or realized stringent price regulation can significantly reduce incentives to innovate and thereby negatively impact future drug development.

R&D for 1980s approvals, and the first study in this series (Hansen, 1979) was mainly relevant to 1970s approvals. While the compound annual growth rates in out-of-pocket costs between successive studies were similar (7.0% per year between the first two studies and 7.6% per year between the last two), the rates of increase for the two major R&D phases were quite different. Although both preclinical and clinical period costs increased in real terms in this study, the rate of increase for the preclinical period was less than one-third that for the first two studies, while the growth rate for clinical costs was nearly twice as high for the two most recent studies.

Our data do not allow us to test hypotheses about factors that affect how costs change over time, but some conjectures can be made. For example, over the periods analyzed the pharmaceutical industry has increasingly focused on developing treatments for chronic and degenerative diseases or conditions associated with those diseases.[52] Therapies for such conditions are generally more costly to test, as they typically require more complex patient care and monitoring, longer periods for effects to be observed, or larger trial sizes to establish their efficacy.

When the study periods analyzed for the previous study and the current one are compared, one observes that the number of new drugs approved increased over time, as did the number of drugs investigated. This can be associated with patient recruitment that is more time-consuming and costlier.

Finally, the development of more stringent cost containment strategies in the United States and abroad such as tiered formularies and the demand for cost-effectiveness results may have led firms to test their drugs more often against competitor products already on the market (F-D-C Reports, 1999). This will generally be costlier than testing against placebo; the trials will likely need to be more highly powered (i.e. clinical trial sizes will have to be higher) to establish a statistical difference.

These factors help explain the growth in clinical period costs. Preclinical (discovery and preclinical development) costs also grew in real terms, but much more slowly than in the past. The widespread use of discovery technologies, such as combinatorial chemistry techniques and high-throughput screening, during the current study period may have created enough efficiency gains to slow down the growth of preclinical costs.

The cost growth rates that we have observed are substantial. There is no guarantee that they will continue at these levels, but we can determine where costs would end up if they did. The average approval date for our sample was in 1997. Assuming the same growth rates for out-of-pocket and capitalized costs, then the out-of-pocket pre-approval cost per approved drug for R&D relevant to approvals in 2001 would be US$ 540 million, while capitalized pre-approval cost would be US$ 1.1 billion. If growth rates were maintained and R&D was initiated in 2001 with approvals obtained 12 years later, then pre-approval out-of-pocket cost would rise to US$ 970 million and pre-approval capitalized cost would rise to US$ 1.9 billion.

A number of technical factors can work to alter the growth pattern for future R&D costs. We observed improved clinical phase attrition rates for the current study. If firms

[52] We have in mind a broader concept than chronic use drugs. The conditions treated may require drugs that are used on a short-term, medium-term, or intermittent basis. These conditions may result from the natural course of a chronic disease or they may occur as side effects from direct treatment of such complex diseases.

can further improve their performance in terminating research early for compounds that will not make it to approval, then this will help lower out-of-pocket and capitalized costs. Reductions in development times, other things being equal, would also lower capitalized costs. Some recent evidence on clinical development times suggest a shortened process, at least in the United States (Kaitin and DiMasi, 2000; DiMasi, 2001a), but it is too soon to conclude that we are observing a new trend. Finally, emerging discovery and development technologies may have profound effects on R&D productivity. Industry analysts that have recently examined the impact that genomics and other new technologies may have on the R&D process have suggested that as pharmaceutical firms increasingly embrace the new approaches, R&D costs may actually rise significantly in the short run (Pharma Marketletter, 2001; Tollman et al., 2001). The major reason is that the new technologies may generate many targets that are currently not well understood. Eventually, though, they argue that the science knowledge base will expand sufficiently so that efficiencies will be realized.

Analyses of private sector R&D costs provide a crucial input to policy-oriented studies. For example, R&D cost estimates can be utilized in studies that aim to measure the ex-post profitability of new drug development for a given period. This is a timely issue given recent media attention on R&D productivity issues and problems in the R&D pipelines of many leading firms (Pollack, 2002). Results from our prior studies have in fact been used in analyses of the rate of return to pharmaceutical R&D (Grabowski and Vernon, 1990; OTA, 1993; Grabowski and Vernon, 1994).[53] These studies of the profitability of new drug development have not found evidence of significant and sustained excess profits. The estimated internal rates of return are quite close to the cost-of-capital. The much higher R&D cost estimates for this study raise a question about the recent profit experience of the pharmaceutical industry. However, Grabowski and Vernon (2000) found substantial growth in pharmaceutical sales for 1990s drug cohorts. A new study (Grabowski et al., 2002) on pharmaceutical profitability using some of the cost results in this study and recent sales data is qualitatively consistent with the outcomes of the earlier profitability studies (i.e. the internal rate of return is close to the industry cost-of-capital).

Data on R&D costs can also be helpful in analyzing the impact on R&D returns from policy changes that affect the intellectual property protection system, drug development times, or FDA approval times, and therefore influence private incentives to innovate. The Congressional Budget Office (CBO), for example, examined the net effect on pharmaceutical industry returns that the *Drug Price Competition Act of 1984* had from simultaneously reducing the cost of generic entry and increasing effective patent lifetimes (CBO, 1998). Simulations of proposed policy changes for these and other variables that affect the costs of and returns to pharmaceutical R&D can similarly be conducted using our new estimates.

The relationship between pharmaceutical industry profitability and investment in R&D has recently been examined in Scherer (2001). The author found a high degree of correlation between the deviations from trend for the time series on pharmaceutical industry R&D expenditures and on gross margins, indicating that R&D outlays are affected significantly

[53] As noted above, tax issues are explicitly considered in such studies. The corporate income tax, however, plays a very limited role in such analyses. The reason is that the tax essentially enters symmetrically in the analysis (applied to revenues as well as costs), and so the impact on the internal rate of return is minimal. The net present value of profits, though, is lower because of the tax.

by changes in profitability. The growth rate for gross margins for recent years was also substantially lower than the growth rate for R&D outlays, leading to the suggestion that R&D growth rates could lessen in the future. If that were to happen, one might ask what would happen to R&D costs. This would depend on the outcome of internal rate of return analyses by firms on marginal projects.[54] The ultimate impact on future costs, however, will also depend on whether and to what degree currently unforeseen biomedical advances that expand scientific opportunities will be realized.

Finally, our results indicate that variability in drug development costs has declined somewhat but is still substantial. For an earlier period, DiMasi et al. (1995a) found varying average clinical period costs for a number of major therapeutic classes. We will examine costs by therapeutic category in future research. For that same earlier period, DiMasi et al. (1995b) also found that average R&D costs tended to decrease with firm size. The structure of the traditional pharmaceutical industry appears to have evolved somewhat since then. Examining new drug output levels by firm, DiMasi (2000) found both a long-term deconcentration trend for the research-based pharmaceutical industry and substantial new entry during the 1990s with respect to traditional small molecule output. The R&D cost data for this study can be used in further analyses of R&D productivity at the firm level in future research.

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New Drug Development:
Estimating entry from human clinical trials

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Abstract

This paper analyses a detailed data set on drugs in human clinical trials around the world between 1989 and 2002. The data provides information on the probabilities with which drugs successfully complete the different phases of the trials and the durations of successful completions. The paper shows that success rates and durations can vary substantially across observable characteristics of the drugs, including primary indication, originating company, route of administration and chemistry. It suggests that analysis of this type of data can help us to answer questions such as: Do AIDS drugs get to market faster? Do Biotech drugs have higher probabilities of getting to market? This paper provides some general statistics for analyzing these questions.

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I. Introduction

The dynamics of drug development is one of the defining characteristics of the pharmaceutical industry. Despite its importance to the industry, there is little information on how long it takes for particular drugs to go through human clinical trials and the probabilities of successful completion. Recently, a number of authors have started making use of historical data on the development of drugs through human clinical trials in the US and elsewhere in the world (for example, Abrantes-Metz, 2003, Kyle, 2002, Danzon et al, 2003). These authors are using this data examine determine the relationship between drug characteristics and successful durations, market entry, and the use of licensing arrangements, respectively. This type of historical data has the potential to provide industry analysts with a much dearer picture of late stage pharmaceutical development and new drug entry. The current paper presents some summary statistics on duration and frequencies of successful completion of the human clinical trials. While this analysis is not sophisticated or detailed enough to provide answers to many of the questions researchers and practitioners are interested in, it does provided readers with some stylized facts to guide future work.

The paper analyzes a sample of drugs that have entered human clinical trials somewhere in the world between 1989 and 2002. The data provides information on entry and exit dates from the three different stages of the human clinical trials for the first indication that the drug was being developed (post-1989). The data also provides information on drug characteristics such as primary indication, chemical composition, route of administration and originating company. The analysis provides frequencies with which drugs with different characteristics successfully complete the different stages of the human clinical trials. For example, drugs that have been originally developed by one of the 10 largest drug companies have a higher than average probability of getting to market. The analysis also provides mean durations for drugs that successfully complete the different stages of the human clinical trials. For example, AIDS drugs are in human clinical trials for an average of 5 years, which is 3 years shorter than the average drug in the sample. In general, the results presented should not be interpreted as causal effects of drug characteristics on success rates or successful durations. Rather these results should be interpreted as central tendencies or simply as statistical observations of the drug development process.

Analysis of drug development and new drug entry must address four major questions. First, do "important" new drugs get through the regulatory process quicker than other drugs? In the US, the FDA offers a number of programs aimed to encourage development of important life-saving drugs, including prioritizing drugs at registration and offering fast tracks through human clinical trials and registration for specified drugs (particularly AIDS drugs). According to the FDA, priority drugs that successfully complete the review process have significantly shorter durations than standard drugs (FDA, 2003). Dranove and Metzler (1994) analyze the FDA's role in drug development durations by analyzing successful duration from discovery to market for US drugs. The authors find that economic indicators seem to be more important in determining durations than "scientific" indicators. This paper and Abrantes-Metz (2003) use more detailed data on the durations and failure rates for drugs in human clinical trials. This paper analyses successful durations through human clinical trials and the governmental review process by primary indication and finds significant differences across different indications. In particular, AIDS drugs and cancer drugs tend to have shorter successful durations. Note that these results should be interpreted with care, as the drugs analyzed are going through different regulatory environments throughout the world.[1] Note also that we have not controlled for the actions of the drug companies and their ability to determine success rates and durations.

Second, are there economies of scale or scope in drug development? Graves and Langowitz (1993) find a positive relationship between R&D expenditures and the number of new chemical entities produced. In their analysis of ten large pharmaceutical firms, Henderson and Cockburn (1996) find a similar relationship between the number of new drug patents and development output. Danzon et al. (2003) find that success rates are increasing with the overall number of drugs the firm has in development and the number of drugs in the relevant therapeutic area.[2] As stated above, the results presented below suggest that drugs discovered by larger companies have a higher probability of getting to market. However, the results also show substantial heterogeneity in the success rates for some of the largest firms. This heterogeneity suggests that firms may have different strategies for investing in drug development.[3] While there may be

[1] See Kyle (2002) for a discussion of the differences across countries.

[2] Danzon et al (2003) discuss the influence that alliances and licenses have on drug development success rates.

[3] It is interesting to consider the similarities between expenditure on new drugs and the expenditure on motion

advantages for larger firms in bringing drugs from discovery to market, it is not obvious that such advantages would be observable. For example, a larger firm may choose a strategy of investing in high risk "blockbuster" drugs. Such a firm may be observed to have a low probability of getting drugs to market, yet may be a very successful company.

Third, what effect does the drug's expected market return have on the probability of success and the time to market? Dranove and Metzler (1994) find that drugs with higher US and World sales have shorter durations to market. Kyle (2003) compares drug entry across countries and indications and finds that the probability of market entry is positively related to market size. DiMasi (2001) reports the results of a survey of drug companies that sponsored drugs through human clinical trials. The survey found that for over 30% of the drugs, whose development was discontinued between 1981 and 1992, the sponsors cited "economic reasons" as the explanation for why development was discontinued. These results suggest that expected market return is an important determinant of success probabilities and durations. The results presented below show that the probability of entry tends to increase with market size, except for drugs destined for very large markets. It is not clear how to interpret such results. One issue is that companies do not randomly choose which drugs to develop, and simple risk/return analysis suggests that companies may try to develop drug with lower probability of getting to market if those drugs are expected to have a higher return. In fact, Danzon et al (2003) find that drugs with a higher expected return have a lower probability of getting to market and argue that this result is consistent with equilibrium behavior. The analysis presented in this paper is not detailed enough to account for such endogeniety issues. The results also show that drugs destined for larger markets tend to spend longer in development. This result seems as odds with our expectation; however it is again not obvious how such results should be interpreted given that durations are heavily influenced by the drug companies.

Fourth, how do the drug's characteristics affect success frequencies and durations? Dranove and Metzler (1994) have some information on how some characteristics affect durations. However, the data is not detailed enough to determine how characteristics affect particular phases of the human clinical trials. The analysis presented in DiMasi (2001) is similar to this paper, however it is done on drugs in

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pictures (Goettler, 2002).

development prior to 1995. A recent change in the industry has been the introduction of biotechnology drugs into human clinical trials. The results show that biotech drugs tend to have higher probabilities of getting to market although their average durations are similar to the average durations over all drugs. The results also suggest significant differences between drugs with different routes of administration (ROA). Oral drugs seem to be quicker to market but with a lower probability of successful completion of human clinical trials. This result is consistent with an equilibrium story that oral drugs have higher expected returns, however these results are not based on a structural estimation so should be interpreted with care. For example, it may simply be the case that it is easier to conduct trials on oral drugs.

The paper proceeds as follows. Section II presents a brief description of the drug development process. Section III describes the data used in the analysis, and provides definitions of the variables used. Section IV presents and discusses the results. Section V concludes.

II. Human Clinical Trials

The process of drug discovery to market can be decomposed into six distinct periods. The first period is commonly known as Preclinical. In general, after preclinical analysis, a company wishing to launch a drug on the US market, for example, files an Investigatory New Drug (IND) application with the FDA. If accepted, the drug goes into human clinical trials, which has three basic phases, called Phase 1, Phase 2 and Phase 3 (the second, third and fourth periods, respectively). An IND may be filled for one or more phases. Generally, the phases are completed sequentially and after the Phase 3 trials have been completed, a company wishing to launch a drug on the US market will file a New Drug Application (NDA) with FDA and move into the fifth period. A drug that passes FDA review successfully is registered in the "Orange Book". Once registered, the drug moves into the sixth period and the company can launch the drug on to the US market. A similar process occurs in other countries.[4]

In preclinical trials, the pharmaceutical company uses genetic analysis, pharmacological tools and "animal models" to test for the safety and the effectiveness of the drug for particular disease indications. Unfortunately, because the data set analyzed below is based on information that is voluntarily given to the

public by the drug's sponsor, the information on preclinical trials is not very accurate. Note that according to the FDA, only 1 in 1,000 drugs pass the preclinical stage and are proposed for testing in humans (FDA, 2002). However, almost half the R&D expenditures occur in the preclinical stage of development (Levy, 1999)

The first phase of the human trials is called Phase 1. Phase 1 trials are generally carried out on a healthy volunteer population of between 20 and 80. According to the FDA, "These studies are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness" (FDA, 2003). Phase 2 trials involve several hundred patients with the disease condition, and are designed to give an early indication of the drugs effectiveness. Phase 3 trials are larger with patient numbers between several hundred and a few thousand, and are designed to give information on the balance between safety and effectiveness (Levy, 1999).

III. Data

Pharmaprojects contains information on 27,987 new branded drug entities that have reached the late stage development from 1980 to 2002. For the purposes of this study, we limited the sample size to the 3,328 drugs that have entered either Phase I, or Phase II, or Phase III of the human clinical trials somewhere in the world for the first time since 1989.[5] Note that information on every stage of development is available for only a limited number of drugs. The data is based on information that is voluntarily provided by the pharmaceutical companies in the form of press releases and academic conferences. Table (1) in the appendix presents information on the number of drugs for which we have information on the different phases of development. Note that of the drugs for which the data

provides information on Phase 3, just less than half have no information on the previous phases. It is thus necessary to be careful about interpreting results for drugs in Phase 1 and Phase 2 as there may be

[4] See Kyle (2003) for discussion of the differences between the drug development process in different countries.
[5] Note that these trials may or may not be taken place in the U.S. under direct FDA supervision.

substantial self-selection bias in the sample.[6] Although not reported, the good news is that most of the censoring of earlier phases occurs in the earlier years of the study (prior to 1994) suggesting that the censoring is not necessarily related to the expected success of the drug, but related to the standard left censoring problem in duration data.[7]

The length of time in each phase is determined by the time between the entry date of the particular phase and the entry date of the next phase. However, for Phase 3, the entry date of the next phase is the date on which the drug was launched somewhere in the world (for the first time). It should be noted that this phase explicitly includes time spent in government review after the Phase 3 clinical trials have ended. The measure of "success" is the probability of completing each phase of development, where successful completion of Phase 1 is defined as entry into Phase 2, similarly for Phase 2. For successful completion of Phase 3, we assume entry on to the US market.[8]

A number of measures are used to provide some information related to the topics discussed in the introduction. In relation to the drug's importance, the major measure is the drugs indication. The indication of the drug is generally its "primary indication", which is defined as the indication for which the drug is further along in its development. Most drugs are taken through human clinical trials for one indication prior to being tested for other indications. However, it should be noted that in the U.S., for example, doctors are free to prescribe approved drugs for any indication. Given this, it may not always be the case that the drug is intended for its "primary indication".

The measure of company size is "Big Pharma". A drug is categorized as either being originally developed by a big pharma firm or a non-big pharma firm. The drug's firm is a big pharma firm if the

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[6] We may therefore expect to see that the drugs in the sample have a higher probability of getting to market than the average drug which enters the particular phase.

[7] In general data from any particular time interval is going to have a "left" censoring and "right" censoring problem. Left censoring refers to the fact that some durations began prior to the beginning of the sample period. Similarly, right censoring refers to durations that end after the end of the sample period. In this case the interval is a lot larger than the average duration for each phase, meaning that the censoring shouldn't be too large of a concern for the phase duration statistics.

[8] We are assuming that the objective of every drug is to be launched on the US market, which may be overstating things and thus we are including drugs that have no intention of going to the US market thus biasing the probabilities downwards.

company's world revenue for 2001 was one of the top ten in the pharmaceutical industry. One concern with using a measure of revenue is that it is endogenously determined, with successful drugs getting to market and creating revenue for the firm.[9] In the results we also report success probabilities and successful durations by individual company for the 8 companies with the largest number of drugs in the data base. In the life of a drug from discovery to market, there are many companies that are involved in its development, human clinical trials and marketing. In the results presented below the only company discussed is the drug's "originator". This is the company, according to Pharmaprojects, that discovered the drug. However, it may not be the company that sponsors the drug through the human clinical trials or takes the drug on to the market.[10] One advantage of using the drug's originator is that to some extent it is exogenous to the likely success of the drug in human clinical trials, particularly as only 1 in 1000 drugs ever makes it from discovery to human clinical trials. A disadvantage is that the originator, particularly a small company, is likely to license the drug to a large company in order for the larger company to take the drug through the trials and on to the market. We therefore may be underestimating the advantage to a drug of being sponsored by a large firm.

The measure of market size is the current world revenue for the drug's therapeutic class and pharmacological description. For example, the market size for the arthritis drug, Celebrex, is equal to the world revenue for arthritis drugs based on the Cox-2 inhibitor. The market size is then categorized into five discrete groups. This is a very crude measure of expected return, particularly as it does not account for the number of drugs in the market.[11] Unfortunately, we don't have more direct measures of market size, such as the actual revenue earned by the drug. We also don't have any information on the cost of drug development.[12] However, one advantage of this measure is that it provides some indication of the market size for drugs that have not yet reached the market.

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[9] Thanks to an anonymous reviewer for pointing this out.

[10] See Danzon et. al (2003) for a discussion of how licensing arrangements are related to success rates.

[11] Kyle (2002) finds that it is important to account for the number of drugs in the market when looking at market entry probabilities.[11] For discussion of drug development costs please see DiMasi et. al. (2003).

[12] For discussion of drug development costs see DiMasi et. al. (2003).

Finally, the data provides a number of other measures of drug characteristics including the drug's route of administration and the drug's original material. The drug's route of administration is categorized by a number of degrees of specificity. For example, a pill is categorized as "alimentary", and then "oral". We report results as specifically as possible while having enough drugs in the category for sensible statistics. The drug's original material is similarly categorized, so a particular biotech drug may be categorized as "biological", and then "recombinant protein". We report the statistics at the highest category level.

Table (2) represents the number of drugs in each phase of development according to their company size, material, route of administration and market size. Since 1989, first time entry drugs number 1,796 for Phase I, 1,879 for Phase II, and 1,025 for Phase III. Of the 398 drugs that have been launched worldwide, only 217 of them have been launched into the US market. 1,465 of the 3,328 drugs in the sample have been withdrawn or discontinued from development.

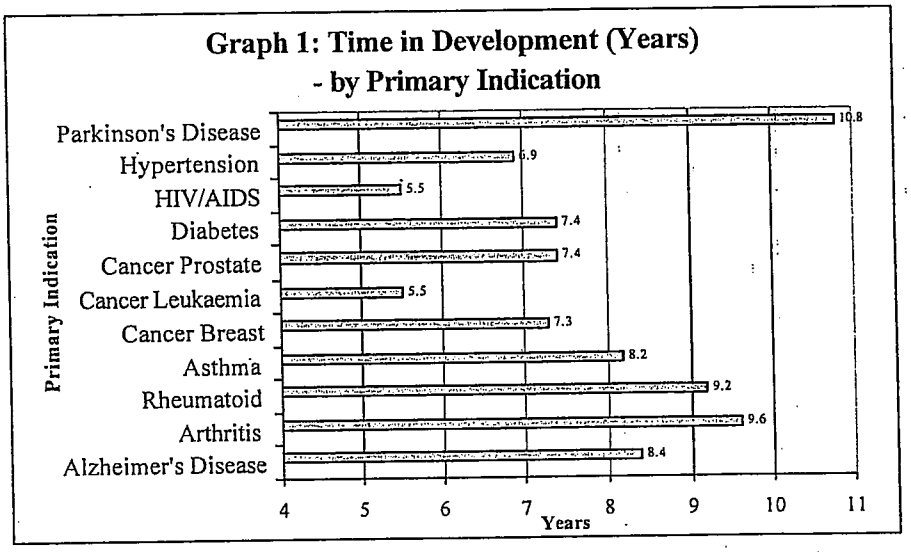
IV. Results

i) Do important drugs get to market faster?

In the US, the FDA has instituted policies that give pharmaceutical companies the opportunity to get "important" drugs to market. These policies include faster review of "priority" drugs and fast-tracking of human clinical trials for certain drugs. Priority drugs are defined by the FDA at the time of registration (generally after the completion of the Phase 3 clinical trials). The FDA also offers the opportunity for some drugs to shorten their time in human clinical trials and in this way, "fast-tracking" drugs to market. Time in development is calculated by adding together the average duration that drugs in the sample spend in each stage of development. On average, it takes just under 8 years for a drug to go from Phase I of human clinical trials to market launch in the US. The same figures for Phase II and Phase III drugs are 6.1 and 3.7 years respectively. More specifically, an average drug spends 1.7 years in Phase I, 2.4 years in Phase II, and 3.7 years in Phase III before launch.

Graph 1 presents a graph showing the estimated duration for the drugs in the data set by their primary indication. While it takes just 5.5 years on average for HIV/AIDS drugs to get from Phase I to the market, it takes drugs for Parkinson's disease almost twice that long to go through the same process. Drugs

for arthritis also spend more than 9 years, and asthma drugs spend more than 8 years in clinical trials on average. HIV/AIDS, anti-hypertension, and leukemia cancer drugs are some drugs that spend less than 7 years in clinical development. Again, this result is suggestive, but more sophisticated analysis is necessary to determine whether more important drugs get to market faster, and why.



ii) Are there economies of scale or scope in drug development?

While the data and the analysis is not nearly detailed enough to get at this question, we can present some summary statistics on the relationship between firm size (as measured by revenue) and success probabilities and successful durations. The probabilities are calculated by multiplying together the estimated probabilities of a drug moving from one particular stage in development to the next stage. The method of calculation can be expressed by the following equation:

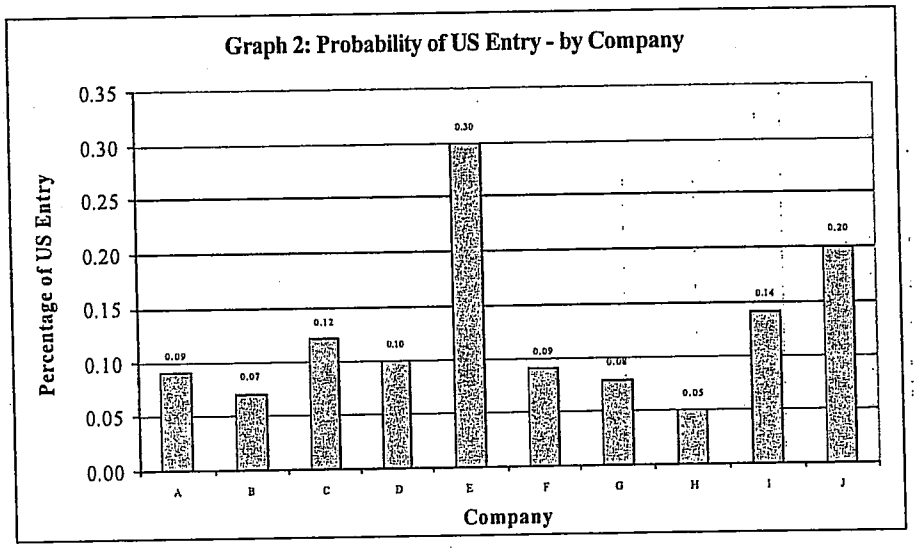
Pr (Launch=1|Phase I=1) = Pr (Launch=1|Phase III =1) x Pr (Phase III=1|Phase II=1) x Pr (Phase II=1|Phase I=1)

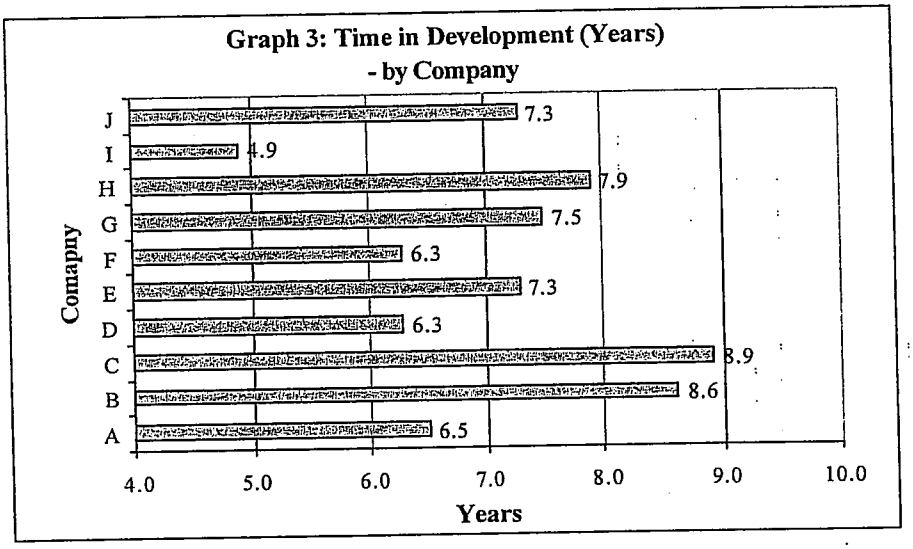
In words: probability of drugs being launched onto the market when they enter Phase I equals the product of the probability of drugs getting from Phase I to Phase II multiplied by the probability of the drugs in Phase II advancing to Phase III, multiplied by the probability of drugs in Phase III being launched onto the US market.

The reason behind this method is that information on all stages of clinical development is available for only a limited number of drugs. By studying this group of drugs exclusively, we would significantly reduce the sample size, and thereby, potentially exclude important information. Instead, we calculate the probabilities of the drugs in each phase of development getting to the next phase from the time they entered Phase I clinical trial until their launch to the market, and then multiplying the results together. The probabilities of drugs moving from a particular stage to the next are calculated using the number of drugs that have advanced to the next stage as numerator, and the sum of drugs that have been suspended, withdrawn or discontinued from that particular stage, or moved on to the next stage as the denominator. Drugs that are still active in that particular stage of development are not used in this calculation.

The results presented in Tables (4) through (9), show that drugs originally developed by Big Pharma firms are more likely to get to market, especially from Phase 3, where Big Pharma drugs have a 47% probability of getting to market, compared to 36% for non-Big Pharma drugs. Tables (5) and (6) show that this pattern holds for particular types of drugs such as drugs indicated for arthritis and drugs indicated for hypertension. In regards to successful durations, overall Big Pharma drugs are slightly quicker to market, but this pattern does not hold for the two subsets of drugs presented in Tables (8) and (9). We should be very careful interpreting such results as suggesting that that there are economies of scale or scope in pharmaceutical development, given both the discussion above on endogeniety and the heterogeneity in both success rates and successful durations for some of the larger companies.

Graphs (2) and (3) suggest that different companies may have different strategies in relation to drug development. It is particularly noteworthy that drugs from Company H have the lowest probability of getting to market, just 5% from Phase 1, and one of the longest successful durations at almost 8 years. On the other hand drugs invented by Company E have very high probabilities of entering the US market at 30% from Phase 1. Again these types of statistics are simply suggestive. We cannot conclude that the heterogeneity is due to such development strategies. We can however conclude that it will be difficult to empirically estimate economies of scale or scope given that company specific development strategies may influence observed probabilities of success.

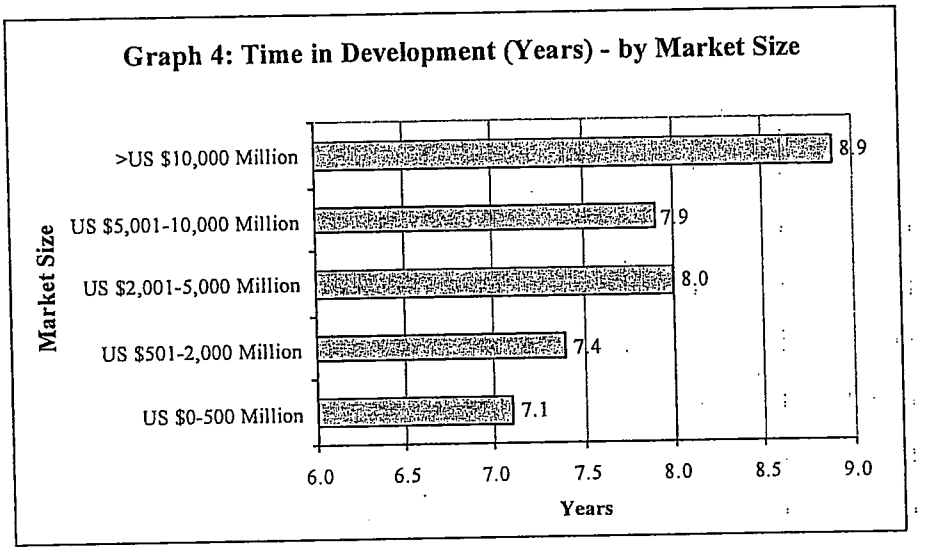




iii) What effect does the drug's expected market return have on success probabilities and durations?

The results presented in Table (4) show that as market size increases from less than $500 million to less than $10 billion, the probability of successfully completing each phase is generally increasing. Drugs with a market size of less than $500 million have just over a 1 in 4 chance of getting to market from Phase 3, while

drugs with markets between $500 million and $2 billion have a almost 1 in 2 probability of getting to market. However, the overall picture is far from clear. There are 100 drugs in Phase 1 that have a market size as being over $10 billion, of these drugs only 4 have reached the market in the US. Tables (5) and (6) present the success rates on two subsets of drugs, those indicated for arthritis and those indicated for hypertension. Arthritis drugs associated with a market size over $5 billion have a less than average probability of getting to market, while similar hypertension drugs have a greater than average probability of getting to market. Finally, it is not clear how to interpret such success rates as in equilibrium we would expect a negative relationship between expected return and successful probabilities (Danzon et. al., 2003).



In regards to successful durations, Graph (4) shows that time in development is generally increasing in market size, with large market drugs taking almost 2 years longer to get to market than small market drugs. The results presented in Tables (8) and (9) shows that this pattern also seems to hold for the two subsets of drugs (arthritis and hypertension). It is again not clear how to interpret such statistics given that companies decide whether or not to end development and how much to spend on continued development, based on their expectation of market return.

iv) What effect do drug characteristics have on success rates and successful durations?

Table (4) presents the success rates in regards to US entry from different phases of development for different categories of route of administration and different original materials. In regards to route of administration, oral drugs seem to have a relatively high probability of getting to market, but drugs delivered by subcutaneous injection have an even higher probability of getting to market. At more general category levels there is not much different between success rates for alimentary drugs and parenteral drugs (injections). In regards to original materials, biologicals seem to have higher success rates than other types of drugs. The most interesting result from Tables (5) and (6) is that almost all intravenous drugs get to market for arthritis, while no intravenous drugs get to market for hypertension. Similarly, a high percentage of biological drugs get to market for arthritis, while there is only one biological in the sample that has been developed for hypertension and that drug did not get passed Phase 1.

Table (7) presents the time in development for drugs with different characteristics. The table shows that drugs that would be relatively easy to administer, including orals, respiratory and transdermal (for example patches), are quicker to market than drugs delivered by injection. In particular, drugs delivered by intramuscular injection take over 9 years to get from Phase 1 to market, while transdermal drugs take less than 7 years to get from Phase 1 to market. It is not clear whether these results indicate that drugs with higher returns will get to market quicker or whether it is simply easier to conduct human clinical trials when drugs have particular routes of administration.

V. Conclusion

Drug development is one of the salient characteristics of the pharmaceutical industry. However, it is not an area of the industry for which we have a lot of information. Recently, a number of authors have started to make use of data on success rates and durations for human clinical trials (Abrantes-Metz et. al., 2003, Danzon et. al., 2003, and Kyle, 2002). This study analyzes the probability of success and the length of successful durations for 3,328 branded drugs that had entered either Phase I, Phase II or Phase III of the human clinical trials somewhere in the world between 1989 and 2002. Our basic summary is that approximately 1 in 8 drugs that entered Phase I are launched on the US market.[13] On average, this part of

[13] Our probability estimate is much lower than the FDA's. This is probably because the sample includes drugs that

the development process takes just under 8 years. This number is close to the FDA's own figure of 8.5 years in their tracking U.S. human clinical trials (FDA, 2002). The complete process of getting a drug to the market can be substantially longer. Bosch and Lee (1994) report that it takes a total of 12 years to get a new drug approval from the FDA. We excluded the preclinical period from our analysis since the Pharmaprojects data set is based on public information, and so focuses on drugs that have already made it to the late stage development.

There four major questions, that studies like this one, may be able to answer. Do more important drugs get to market quicker? Are there economies of scale or scope in drug development? What effect does the expected return have on the drug's development? What effect do characteristics of the drug have on the drug's development? We do find that HIV/AIDS drugs get to market quicker than the average drug. We find that drugs originally developed by the 10 largest pharmaceutical companies have slightly lower probabilities of US entry from Phase I, but spend substantially less time in all clinical development phases than the average drug. Drugs with the potential for extremely lucrative markets of US $10 billion or more tend to spend more time in development, and have a lower probability of actually reaching the market. Biological drugs have some what higher probabilities of making it to the US market, but this may vary across indications.

The results give, at best, partial answers to these questions. In some cases the results seem unintuitive, but as discussed above, answering these questions is quite complicated and requires careful analysis of these newly available data sets. It is hoped that the results discussed above increase our knowledge of the industry and create interest in more sophisticated econometric analysis such as that presented in Abrantes-Metz et al. (2003).

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were never intended for the U.S. market.

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APPENDIX

Table 1: Drugs That Appear in Each Phase of Development

	Number	Percent
Phase 1 only	931	28%
Phase 2 only	786	24%
Phase 3 only	466	14%
Phase 1 and Phase 2 only	586	18%
Phase 1 and Phase 3 only	52	2%
Phase 2 and Phase 3 only	280	8%
Phase 1, Phase 2 and Phase 3	227	7%
Total	3328	100%

Table 2: Number of Drugs by Category

	Phase 1	Phase 2	Phase 3	US Launch	World Launch	Ceased
Big Pharma	268	304	176	60	80	339
Non Big Pharma	1528	1575	849	157	318	1126
Material						
Biologicals	450	387	187	43	81	165
Chemicals	932	1046	664	159	279	612
Natural Products	66	80	60	13	21	44
ROA						
Alimentary	403	487	372	103	161	222
Parenteral	492	539	323	76	141	219
Respiratory	48	56	21	5	9	29
Topical	64	68	71	22	38	37
Transdermal	28	28	26	5	9	22
Novelty						
Not Available	931	944	353	21	31	1465
All Preclinical	4	2	2	0	0	0
Established Strategy	178	210	212	74	153	0
New Formulation	84	104	115	29	57	0
Low Novelty	56	22	5	0	0	0
2nd, 3rd or 4th Compound	156	139	59	0	0	0
Leading Compound	387	459	279	93	157	0
Market Size						
US $0-500 Million	169	206	121	20	41	157
US $501-2,000 Million	521	581	330	94	144	436
US $2,001-5,000 Million	694	647	339	64	123	487
US $5,001-10,000 Million	230	259	123	28	58	222
> US $10,000 Million	138	154	91	7	22	141
Drug Age (Years)	**12.8**	**13.9**	**15.4**	**15.9**	**16.2**	**15.9**
(Standard Deviation)	(5.0)	(5.0)	(5.4)	(5.7)	(5.1)	(4.4)
N	**1796**	**1879**	**1025**	**217**	**398**	**1465**

Table 3: Primary Indication - Number of Drugs by Category

		Phase 1	Phase 2	Phase 3	US Launch	World Launch	Ceased
Alzheimer's Disease		22	31	13	2	2	26
Arthritis Rheumatoid		29	34	11	5	6	15
Asthma		42	49	18	4	8	29
Cancer							
	Breast	34	34	17	3	9	17
	Leukemia	15	22	9	5	6	12
	Lung	34	34	10	0	1	9
	Prostate	16	19	12	3	3	2
Diabetes		39	39	21	6	7	14
Hepatitis		26	21	11	3	7	6
HIV/AIDS		46	58	29	14	15	36
Hypertension		29	41	41	10	23	26
Parkinson's Disease		19	20	12	4	5	8
Thrombosis		28	31	17	4	8	23
N		**1796**	**1879**	**1025**	**217**	**398**	**1465**

Table 4: Probability of US Entry of Clinically Developed Drugs from Phase of Development (Number of Drugs in the Sample)

		Phase 1	Phase 2	Phase 3
All Drugs		**0.12**	**0.17**	**0.38**
		(1366)	(1218)	(542)
Big Pharma		**0.10**	**0.17**	**0.47**
		(217)	(219)	(127)
Non Big Pharma		**0.12**	**0.17**	**0.36**
		(1149)	(999)	(415)
Biologicals		**0.25**	**0.31**	**0.53**
		(309)	(218)	(75)
Chemicals		**0.19**	**0.25**	**0.45**
		(725)	(664)	(343)
Natural Products		**0.18**	**0.23**	**0.37**
		(50)	(45)	(30)
Alimentary		**0.28**	**0.34**	**0.51**
		(301)	(308)	(200)
	Oral	**0.29**	**0.35**	**0.51**
		(290)	(296)	(197)
Parenteral		**0.28**	**0.32**	**0.49**
		(405)	(343)	(147)
	Intravenous	**0.30**	**0.34**	**0.48**
		(209)	(195)	(86)
	Subcutaneous	**0.43**	**0.45**	**0.61**
		(43)	(39)	(18)
	Intramuscular	**0.39**	**0.45**	**0.69**
		(36)	(23)	(13)
Respiratory		**0.17**	**0.25**	**0.67**
		(36)	(27)	(6)
Topical		**0.27**	**0.37**	**0.50**
		(49)	(38)	(42)
Transdermal		**0.13**	**0.21**	**0.44**
		(23)	(17)	(9)
US $0-500 Million		**0.09**	**0.13**	**0.26**
		(133)	(128)	(69)
US $501-2,000 Million		**0.16**	**0.23**	**0.47**
		(418)	(391)	(186)
US $2,001-5,000 Million		**0.13**	**0.19**	**0.40**
		(506)	(400)	(159)
US $5,001-10,000 Million		**0.09**	**0.14**	**0.44**
		(178)	(172)	(64)
> US $10,000 Million		**0.04**	**0.06**	**0.13**

	(100)	(110)	(55)

Table 5: Probability of US Entry from Phase of Development (Number of Drugs in the Sample) - Arthritis*

	Phase 1	Phase 2	Phase 3
All Drugs	**0.30**	**0.36**	**0.61**
	(42)	(34)	(18)
Big Pharma	**0.43**	**0.57**	**1.00**
	(4)	(7)	(4)
Biologicals	**0.60**	**0.67**	**1.00**
	(20)	(12)	(3)
Chemicals	**0.24**	**0.32**	**0.62**
	(21)	(21)	(13)
Orals	**0.32**	**0.35**	**0.56**
	(11)	(16)	(9)
Intravenous**	**0.83**	**0.83**	**0.83**
	(9)	(4)	(6)
Large Market	**0.19**	**0.29**	**0.50**
	(12)	(12)	(10)

*By any Indication
** All Drugs Went Through Clinical Phases of Development

Table 6: Probability of US Entry from Phase of Development (Number of Drugs in the Sample) - Hypertension*

	Phase 1	Phase 2	Phase 3
All Drugs	**0.22**	**0.28**	**0.46**
	(34)	(41)	(28)
Big Pharma	**0.27**	**0.38**	**0.57**
	(7)	(6)	(7)
Biologicals**	**0.00**	**0.00**	**0.00**
	(1)	(0)	(0)
Chemicals	**0.25**	**0.32**	**0.46**
	(28)	(34)	(14)
Orals	**0.29**	**0.35**	**0.52**
	(17)	(27)	(16)

Intravenous**	**0.00** (5)	**0.00** (6)	**0.00** (2)
Large Market	**0.30** (25)	**0.37** (31)	**0.58** (19)

*By any Indication
**No Drugs Have Made to the Market

Table 7: Time in Development (Years)

		Phase 1	Phase 2	Phase 3
All Drugs		7.8	6.1	3.7
Big Pharma		7.1	5.5	3.4
Non Big Pharma		8.0	6.4	3.9
Biologicals		8.0	6.4	3.7
Chemicals		7.7	6.1	3.7
Natural Products		7.3	5.5	3.9
Alimentary		7.5	5.8	3.5
	Oral	7.5	5.8	3.5
Parenteral		8.2	6.6	4.0
	Intravenous	7.9	6.3	3.7
	Subcutaneous	8.7	7.1	4.2
	Intramuscular	9.2	7.4	4.6
Respiratory		6.7	5.1	3.3
Topical		7.7	6.4	4.5
Transdermal		6.8	4.9	2.9
N		**1796**	**1879**	**1025**

Table 8: Time in Development (Years) - Arthritis**

	Phase 1	Phase 2	Phase 3
All Drugs	7.9	6.4	3.7
Big Pharma	8.3	6.9	3.8
Biologicals	5.8	4.5	2.1
Chemicals	9.2	7.1	4.4
Orals	8.4	6.5	3.5
Intravenous	NA*	NA*	4.3
Large Market	9.5	8.0	4.8
N	**55**	**63**	**31**

**By any Indication

* Number of observations is insufficient for calculation

Table 9: Time in Development (Years) - Hypertension**

	Phase 1	Phase 2	Phase 3
All Drugs	7.3	6.4	3.2
Big Pharma	7.5	6.4	3.2
Biologicals	NA*	NA*	NA*
Chemicals	7.3	6.5	3.2
Orals	6.4	5.6	3.2
Intravenous	NA*	NA*	NA*
Large Market	7.1	6.4	3.4

N	35	50	47

**By any Indication

* Number of observations is insufficient for calculation

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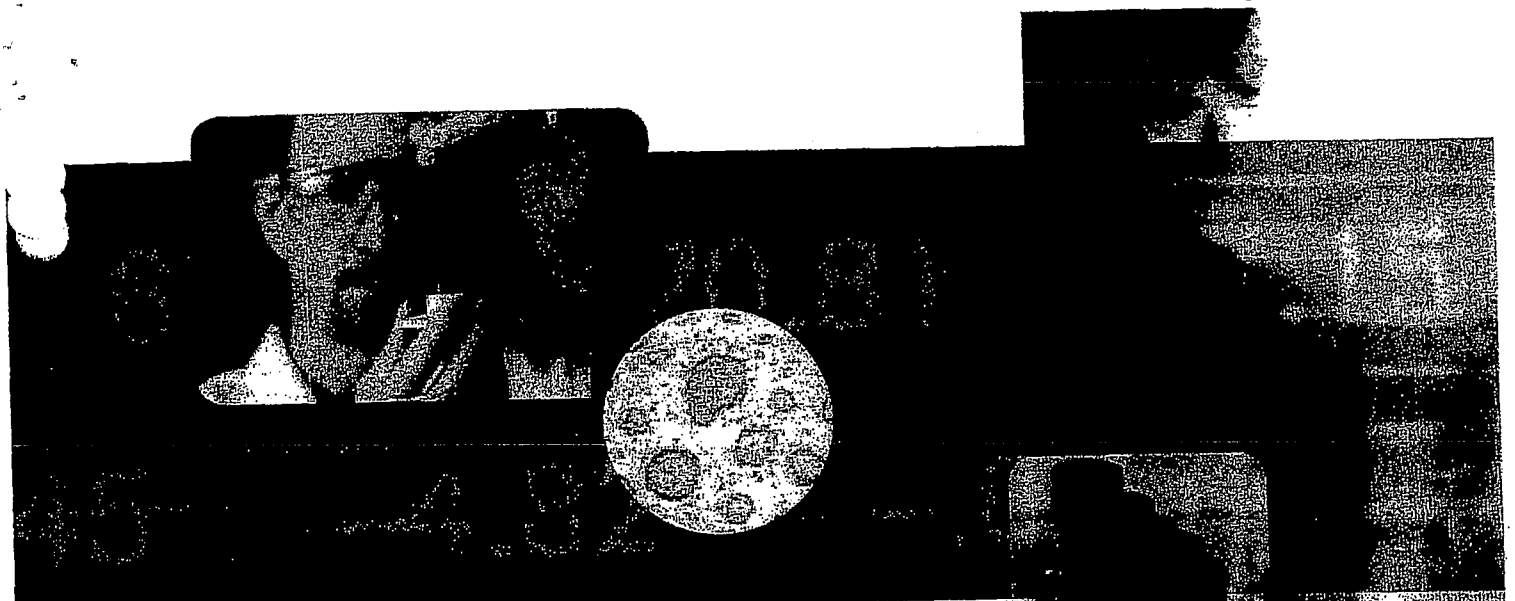


A SAFER STRATEGY:

Investing in biotech stocks is a risky business, but there's safety (as well as big rewards) in numbers.

BY SALIM KANJI, GILLES LAMARCHE, AND JEAN SASSEVILLE

THE BIOTECH SECTOR is a very enticing place to put your investment dollar. After all, if a biotech company succeeds in commercializing an important drug, it can reap hundreds of millions of dollars, even billions, cheered on by its lucky investors. But the risks are many. The wise investor must weigh a given drug's potential profitability against its chances of success in clinical trials. He must balance innovation with investment security and minimize risks with an appropriately sized and diversified portfolio.

INVESTING IN BIOTECH •

The sector, though historically unpredictable, has recently shown even more volatility, with valuation swings that have scared away investors. This is not a situation a sector poised for tremendous growth can afford to be in. Recent advances in *in silico* modeling, high throughput screening, the mapping of the genome, and proteomics have created more opportunities for developing new drugs than ever before.

Additionally, Big Pharma's appetite for compounds that reach proof of concept is insatiable. There will be no shortage of new drugs on the supply side. On the demand side, new emerging middle classes with more disposable income in developing areas such as China, India, Russia, and Eastern Europe offer more opportunities for newly discovered therapies, especially where a substantial unmet need currently exists.

Not to be neglected are the increasing numbers of well-off, aging, and obese baby boomers (the obesity rate has increased to 30 percent in baby boomers, compared with 19 percent in the previous generation, according to Health Canada) in developed economies who will require more diagnostics and therapies for their well-being, part of which will be paid by public health care budgets. In most developed countries, such as the United States and Canada, government health care programs cover about 40 percent of medical costs and private insurance between 40 percent and 50 percent. The rest is covered by individual cash payments.

Greater productivity, increased demand, and biopharmaceutical breakthroughs are on the horizon. With those factors come increased commercialization and marketing of medical products and services. In the context of the worldwide growth in disposable income, clarifying the risks involved results in better ways to measure and evaluate them. More accurate, less volatile valuations in the biotech sector would increase the pool of willing investors and increase the overall profit of such investments.

ISTOCKPHOTO / BONOTOM STUDIO

Current Biotech Landscape

It's been said that biotech is a crapshoot. What are your chances at the biotech table? Using basic statistical analysis—primarily binomial distribution—we've attempted to shed some light on this question by investigating the risk profile of compounds in clinical development by basket size.

Simply put, the four stages of the drug development process are:

- Research and development;
- Pre-clinical testing;
- Phases I, II, and III of clinical trials;
- Filing, approval, and commercialization.

Our focus is on compounds going from phase I to phase III, in accordance with the standard business model of biotech companies, to sell or license them to Big Pharma at phase III. Throughout the article, we've used the cumulative probability of 14.9 percent, meaning that a compound will successfully pass through phases I, II, and III with a probability of 14.9 percent, unless otherwise stated.

This percentage was derived from the development probabilities, as shown in Table 1, that were obtained primarily from Dr. Joseph A. DiMasi's study "The Price of Innovation: New Estimates of Drug Development Costs," from the Tufts Center for the Study of Drug Development. These data were combined with Pharmaprojects' R&D Timelines and analysis by the Frankel Group, with some input from Decision Resources.

There are two noteworthy deviations in Table 1 from the DiMasi study. The phase I probability of 62.5 percent

TABLE 1: **Tufts Study Summary**

(Development probabilities of compounds successfully completing the various phases. Determined from a mix of Tufts DiMasi published data, Pharmaprojects, and analysis from the Frankel Group and Decision Resources.)

Phase	Probability of Success	Cumulative Probability
P-I	62.5%	62.5%
P-II	35.0%	21.9%
P-III	68.0%	14.9%
File	90.0%	13.4%

TABLE 2: **For Baskets of Preclinical Compounds Entering Phase I, the Probability of at Least X Compounds Successfully Completing Phase III**

Basket Size	1	2	3	4	5
1	14.9%	0.0%	0.0%	0.0%	0.0%
2	27.6%	2.2%	0.0%	0.0%	0.0%
3	38.4%	6.0%	0.3%	0.0%	0.0%
4	47.5%	10.7%	1.1%	0.0%	0.0%
5	55.4%	16.3%	2.6%	0.0%	0.0%
6	62.0%	22.1%	4.6%	0.6%	0.0%
7	67.7%	28.0%	7.2%	1.2%	0.1%
8	72.5%	33.9%	10.3%	2.1%	0.3%
9	76.6%	39.7%	13.9%	3.3%	0.5%

TABLE 3: **For Baskets of Preclinical Compounds Entering Phase I, the Probability of at Least X Compounds Successfully Completing Phase III**

Basket Size	1	2	3	4	5
10	80.1%	45.2%	17.7%	4.9%	1.0%
15	91.1%	67.7%	39.1%	17.4%	6.0%
20	96.0%	82.1%	59.0%	34.7%	16.7%
25	98.2%	90.5%	74.2%	52.3%	31.2%
30	99.2%	95.0%	84.5%	67.3%	46.9%
35	99.6%	97.5%	91.0%	78.6%	61.3%
40	99.8%	98.7%	95.0%	86.6%	73.1%

TABLE 4: **For 25 Preclinical Compounds Entering Phase I, the Probability of at Least X Compounds Sucessfully Completing Phase III**

25 Compounds	1	2	3	4	5
90% of Tufts	92.4%	71.6%	44.7%	22.4%	9.1%
Tufts	98.2%	90.5%	74.2%	52.3%	31.2%
110% of Tufts	99.8%	98.3%	93.3%	82.7%	66.3%

is supported by the other sources and is lower than DiMasi's 71 percent. We also split out the filing probability from DiMasi's combined phase III/filing category.

Excluding Big Pharma and several large biotech companies, the vast majority of biopharmaceutical companies have only a few compounds in clinical development, principally because of limited financial and scientific resources. These smaller firms were either founded as a company to develop very specific types of compounds, or they haven't raised sufficient funding to do more. As Table 2 shows, given the 14.9 percent probability of one compound's success through all phases of development, smaller baskets of compounds carry more risk for investors.

The bigger the basket size, the better the expected results. As the number of compounds in the basket increases, so does the probability of having one or more winners. A basket of four compounds gives a nearly even chance that there is at least one winner. But it also means that there is more than a 50 percent chance that there are no winners at all. And this is for four compounds.

At nine compounds, the basket starts to show a greater than 75 percent probability that we'll have one or more winners. But is this good enough? Is the risk acceptable? And what are the implications of this for companies with only one or two development projects?

Phase Success Probabilities

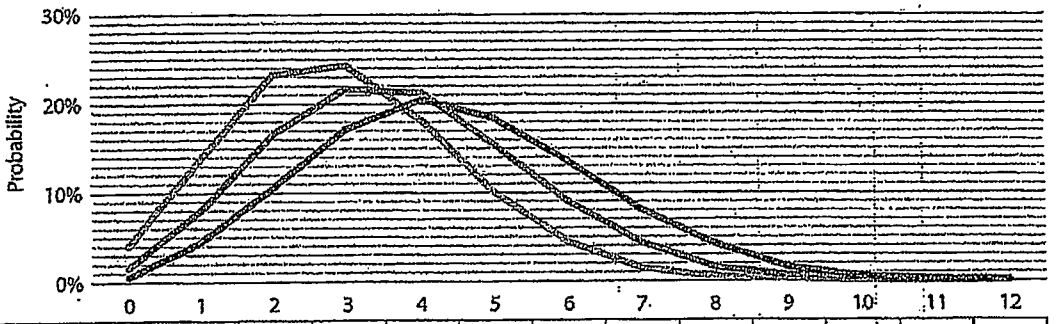
What happens where we have basket sizes that are much larger? Table 3 shows that the risk of total loss, meaning the probability of having no winners, diminishes drastically. And Graph 1 illustrates the particular smoothness of the normal curves in the 20- to 30-compound range of development projects. Where we have 25 development projects, the probability of having no winners is under 2 percent, and the chances of getting three or more winners is almost 75 percent.

The analysis so far has used 14.9 percent as the base cumulative probability of getting from phases I through III. Changing this variable has a dramatic effect on other factors in the risk calculation. Graph 2 shows the impact of a 10 percent improvement and a 10 percent degradation on a basket of 25 compounds under development, compared with the Tufts study's cumulative probability of 14.9 percent. This means each phase probability is increased by 10 percent, giving a cumulative probability of 21.8 percent instead of 14.9 percent. According to Table 4, which shows the impact on the cumulative probabilities, improving the success rates for each phase has a bigger impact in reducing risk than adding more development projects.

Going Forward

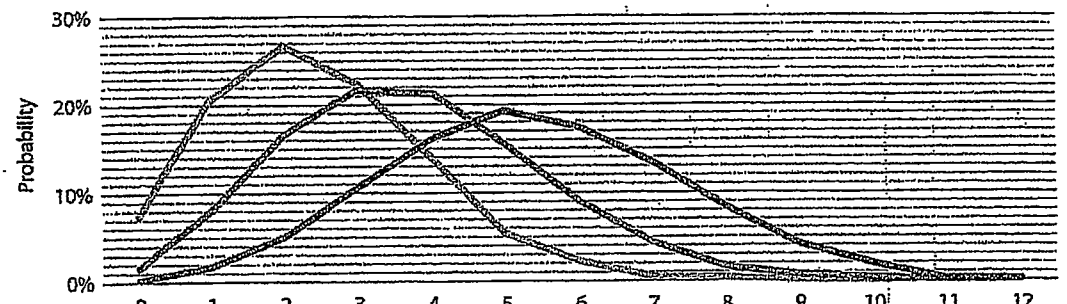
Statistical analyses like this one assume randomness and independence, and provide a way to compare basket sizes, all other things being equal. But we know that the probability of success depends not only on basket size but also on the types of compounds studied and the nature of the conditions they're meant to target. For instance, a given compound may belong to a family that has been proven to have minimal adverse effects and therefore has a much higher probability of success. Comprehensive statistics, therapeutic area, geographical region, molecular groupings by class, and so forth would be tremendously useful in further refining the evaluations.

GRAPH 1. **Probabilities for Phase III Completion**



	0	1	2	3	4	5	6	7	8	9	10	11	12
20 compounds	4.0%	13.9%	23.1%	24.3%	18.1%	10.1%	4.4%	1.5%	0.4%	0.1%	0.0%	0.0%	0.0%
25 compounds	1.8%	7.8%	16.3%	21.9%	21.1%	15.5%	9.0%	4.3%	1.7%	0.6%	0.2%	0.0%	0.0%
30 compounds	0.8%	4.2%	10.6%	17.2%	20.4%	18.5%	13.5%	8.1%	4.1%	1.7%	0.6%	0.2%	0.1%

GRAPH 2. **Probabilities for Phase III Completion**



	0	1	2	3	4	5	6	7	8	9	10	11	12
90% of Tufts	7.6%	20.7%	26.9%	22.3%	13.3%	6.1%	2.2%	0.6%	0.2%	0.0%	0.0%	0.0%	0.0%
Tufts	1.8%	7.8%	16.3%	21.9%	21.1%	15.5%	9.0%	4.3%	1.7%	0.6%	0.2%	0.0%	0.0%
110% of Tufts	0.2%	1.5%	5.0%	10.6%	16.3%	19.1%	17.8%	13.5%	8.4%	4.4%	2.0%	0.8%	0.2%

This study doesn't address the potential market opportunity for a given compound, the timing of its research and release, and the probability of its commercialization. These questions should be addressed in a separate study that integrates this statistical analysis, to ultimately determine risk/return levels. We're presently exploring a methodology for an actuarial valuation of compounds in clinical development in terms of probability outcomes as well as financial risk/reward elements.

We separately compared a stock-picking fund with a direct basket of compounds in development, but as expected, as long as the total number of compounds covered was the same, there was no significant statistical difference between them. For example, a stock-picking fund that has invested in a group of 10 biotech companies, which in aggregate encompasses 25 development projects in the clinic, has essentially the same chance of getting winners as a basket of 25 compounds.

There are other significant differences, though, that haven't been factored into this review. For one thing, the overheads and other related expenses for running 10 companies instead of one differ significantly. Moreover, the general stock market risks of fickle valuations, fraudulent manipulation of stocks, and potential mismanagement are multiplied over 10 companies.

We submit that the merger of various smaller biotech entities into one provides a better risk posture for investors. Furthermore, given our results, investors interested in developing products in the clinic should invest directly in selected compounds of interest, maximizing their success and overall return on investment. The current "one in five" model, meaning that only one in five biotech companies will survive, has to go.

To prosper, the biopharmaceutical industry must consolidate its components and diversify its investment vehicles, or it's likely to lose many of its key investors to less volatile markets. ●

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IN THE UNITED STATES DISTRICT COURT
FOR THE
DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY, and MANULIFE INSURANCE COMPANY (f\k\a INVESTORS PARTNER INSURANCE COMPANY), Plaintiffs, v. ABBOTT LABORATORIES, Defendant,	CIVIL ACTION NO. 05-11150-DPW

UPDATED EXPERT REPORT OF ALAN FRIEDMAN

DECEMBER 3, 2007

Highly Confidential - Subject to Protective Order

INTRODUCTION

1. The following is the updated expert report of Alan Friedman, Vice President of CRA International, ("CRA"), submitted in connection with John Hancock Life Insurance Company, John Hancock Variable Life Insurance Company, and Manulife Insurance Company (f\k\a Investors Partner Insurance Company) v. Abbott Laboratories. (Civil Action No. 05-11150-DPW). This updated report considers the additional and updated information I have received and analyzed since the filing of my initial report on October 13, 2006 (prior to the close of fact discovery).

2. I have been asked by Choate, Hall & Stewart LLP, on behalf of John Hancock Life Insurance Company, John Hancock Variable Life Insurance Company, and Manulife Insurance Company, (collectively "John Hancock"), to calculate damages, if any, resulting from alleged fraud and breach of the Research Funding Agreement dated March 13, 2001 ("the Agreement") by Abbott Laboratories ("Abbott").

3. I have been responsible for CRA's efforts in connection with this matter and expect to be called to testify as an expert witness at the trial. This report summarizes the contents of my opinions to date and is a summary of my expected testimony. I reserve the right to render additional opinions and to supplement or further update this report to the extent permitted by the court based upon ongoing analysis, or as may be required by events that may occur in the course of this litigation, such as production of additional documents and deposition or trial testimony. I expect to prepare and utilize demonstratives at trial that will aid me in explaining my analysis and opinions in this matter. These demonstratives have not yet been prepared.

4. For the purpose of my analysis, I have assumed that Abbott has breached its obligations to John Hancock under the Agreement. I have also assumed that Abbott misrepresented or failed to disclose material information with respect to certain compounds that are the subject of the Agreement for the purpose of inducing John Hancock to enter into the Agreement and to make various payments to Abbott in accordance with the terms stated therein.

Qualifications and Testimony

5. CRA International has provided expertise in economics, finance and business strategy for over 40 years. The finance practice of CRA provides financial, economic and accounting expert analysis, testimony, and support in litigation and regulatory proceedings. I have over 25 years of experience in the financial consulting area. Prior to joining CRA, I was President of Friedman, Turbidy & Company, a business consulting firm. Prior to that, I was a Partner in the Consulting Division of Deloitte & Touche where I held leadership roles in the national Litigation and Mergers & Acquisitions practice. I have been retained as an expert witness and consultant in over 60 litigation matters and have testified in Federal court, arbitrations and mediations on the subject of damages in matters involving breach of contract, financings, acquisitions and intellectual property. In the medical products arena, I have been retained as an expert witness and/or consultant in cases involving medical devices and pharmaceutical products. I have also assisted clients in breach of contract and fraud cases. My curriculum vitae and a list of my testimonial experience during the last four years are attached as Exhibits 1.1 and 1.2, respectively.

Compensation

6. CRA is being compensated on an hourly basis for the work my staff and I perform. My billing rate is $550 per hour; rates of other CRA personnel assigned to this project range from $85 to $405 per hour. This compensation is unrelated to the outcome of this matter.

Documents Considered

7. As part of my work on this matter, I have considered legal filings and documents produced in this case, various analyst reports, and publicly available literature. I have also considered various deposition transcripts. A listing of information sources I have considered to date is attached as Exhibit 1.3.[1]

SUMMARY OF OPINIONS

8. Based on the analysis presented in this report and the updated information that I have received since my initial report, I have computed the damages[2] to John Hancock relating to ABT-518, ABT-594, and ABT-773 to be between $238 and $369 million, as follows:[3]
   - $221 to $355 million in lost royalty payments; and
   - $17 to $13 million in lost milestone payments.

9. Based upon actual spending information produced by Abbott, and independent of the lost royalty and milestone analysis, I have also computed damages associated with a shortfall in Abbott's Program Spending to be between $28.3 and $33.0 million, not including pre-judgment interest.[4]

10. I have considered that if ABT-518, ABT-594, and ABT-773 (the "Misrepresented Compounds") were *actually* viable compounds as represented by Abbott at the time of the Agreement, then additional research and development spending on these compounds would likely have been incurred. Based on this "*But-for*" scenario, the damages related to the shortfall in Abbott's program spending would be eliminated.

[1] Since October 13, 2006, I have been provided with numerous documents and material information obtained through discovery that have caused me to update my report. This information includes depositions and legal filings, along with updated information as to the development status and Abbott's reported spending on the Program Compounds. All of the additional materials and information that I have considered is included in Exhibit 1.3

[2] My updated calculation of damages attributable to lost royalty and milestone payments takes into account Abbott's termination of Program Compounds ABY-627 and ABT-510, which was reported by Abbott after my initial report. The damage amounts presented reflect the nominal value of past damages plus the present value of future damages, estimated as of December 31, 2007. My calculation of pre-judgment interest as of the same date is included in Exhibit 3.1 and Exhibit 4.1.

[3] Differences are due to rounding.

[4] I have updated my Spending Shortfall analysis based on new information produced by Abbott, including the Abbott Laboratories' Amended Responses and Objections to Plaintiff's 2nd Set of Interrogatories (August 3, 2007) and the 2008 Annual Research Plan (November 20, 2007). (See Exhibit 6.1). My computation of pre-judgment interest on the Program Spending shortfall damages is included in Exhibit 6.1.

11. I understand that the Court has already ruled, and that the U.S. Court of Appeals has affirmed, that John Hancock is not required to make the 2003 and 2004 Program Payments of $58 million and $52 million, respectively. I have considered, however, that if the Misrepresented Compounds were *actually* viable compounds as shown in Abbott documents at the time of the Agreement, then the 2003 and 2004 Annual Research Plans may also have forecast Program Term spending in excess of the $614 million Aggregate Spending Target. I have computed numerous Program Funding scenarios, which, on a probability-weighted basis, imply expected Program Payments of $33.6 million (2003) and $41.7 million (2004) for the Base Case. The expected Program Payments in the Low Case are $21.0 million (2003) and $36.8 million (2004).[5,6] (See Exhibits 9.1 – 9.4). My updated analysis regarding expected Program Payments would serve as a potential offset to the John Hancock's damages I have computed in this case.

12. I have also determined that in the event that a rescission of the Agreement is ordered, Abbott would owe to John Hancock approximately $90 million, which reflects a return of invested money less management fees and royalties paid to date, but not including pre-judgment interest.[7] (See Exhibit 7.1).

13. I have not quantified the impact that out-licensing activity related to the Misrepresented Compounds might have on my computation of damages. Depending on future events, I may conduct such an analysis.[8]

14. As part of Hancock's response to Abbott's Third Set of Interrogatories (dated April 30, 2007), I provided damage estimates on a compound-by-compound basis. Subsequent to the updated analyses contained in this report, I have also updated the information included in those interrogatory responses as set forth in attached Exhibits 8.1, 8.2, and 8.3.

[5] Based upon statements made by head of Abbott's Portfolio Analysis Group, Mr. Keith Hendricks, at his deposition on April 27, 2007 (pp. 109-114) and updated information that I have received concerning Abbott's reported actual spending and its reasonably expected spending, my updated analysis shows that by December 2001 (after Abbott submitted its 2002 Research Plan to Hancock), and assuming that Abbott intended to terminate ABT-773, Abbott did not reasonably expect to spend $614 million on Program Compounds throughout the Program Term. This suggests that Hancock may not have been required to make its second Program Payment of $54 million in the "Actual" world.

[6] Expected payment amounts computed reflect the nominal value. Pre-judgment interest computed on these amounts is included in Exhibits 9.1 – 9.4.

[7] My computation of pre-judgment interest under a Rescission scenario is included in Exhibit 7.1.

[8] As of the date of this report, and for calculation purposes, I assume that ABT-773 will yield no royalty or milestone payments to John Hancock. However, if Abbott's out-licensing of any of the Misrepresented Compounds, including ABT-773, results in actual royalty or milestone payments to John Hancock, such payments will reduce damages computed for those compounds on an equivalent dollar-for-dollar basis. Alternatively, if Hancock is fully compensated for its damages related to specific compounds, then I assume that Hancock would not receive additional payments related to the future success of those compounds.

CASE BACKGROUND

The Parties

15. Plaintiff John Hancock Life Insurance Company is a wholly-owned, indirect subsidiary of Manulife Financial Corporation. The company maintains its headquarters in Boston, Massachusetts and provides a broad array of insurance and investment products to retail and institutional customers, primarily in North America. Plaintiff John Hancock Variable Life Insurance Company is a wholly-owned, direct subsidiary of John Hancock Life Insurance Company, and also maintains headquarters in Boston, Massachusetts and provides a range of insurance and investment products. Plaintiff Manulife Insurance Company (f/k/a Investors Partner Insurance Company) is a wholly-owned, direct subsidiary of plaintiff John Hancock Variable Life Insurance Company.[9]

16. Abbott Laboratories is a corporation that is based in Abbott Park, Illinois. Abbott is a healthcare company that discovers, develops, manufactures and markets products and services that evolve around care, from prevention and diagnosis to treatment and cure. Abbott's principal businesses are global pharmaceuticals, nutritional products, and medical products, including diagnostic and cardiovascular devices. In order to finance its activities and its research and development efforts Abbott utilizes funding from its internal sources, and on occasion, funds from external sources.[10]

The Research Funding Agreement

17. On March 13, 2001, John Hancock and Abbott entered the Agreement, whereby John Hancock agreed to provide funding to Abbott for research and development activities on a portfolio of nine pharmaceutical compounds (the "Research Program" and "Program Compounds" respectively) in exchange for the right to receive certain management fees, future milestone and royalty payments from Abbott.[11]

18. Under the terms of the Agreement, John Hancock agreed to contribute up to a specified maximum amount toward the costs incurred by Abbott in operating the Research Program ("Program Related Costs") in four annual installments over the period from December 1, 2001 through December 1, 2004. Abbott agreed to invest at least twice the amount of John Hancock's contribution from its own funds toward the operation of the Research Program, and committed to spend certain minimum amounts on Program Related Costs during each year of the Research Program, as well as a minimum aggregate total over the four-year term of the Research Program, March 13, 2001 through December 31, 2004.[12]

The Misrepresented Program Compounds

19. It is my understanding that as of March 13, 2001, the date the Agreement was executed, Abbott had material information regarding at least three of the nine Program Compounds that it did not disclose to John Hancock. The undisclosed information was adverse. Ultimately, Abbott

[9] See www.johnhancock.com
[10] See www.abbott.com
[11] JH 008078 – 008211, Research Funding Agreement
[12] JH 008078 – 008211, Research Funding Agreement, Articles 3.2 and 3.4

officially suspended its development of at least three Program Compounds for which it had undisclosed information: ABT-518, ABT-594, and ABT-773, the Misrepresented Compounds.[13]

20. I have conducted analyses to assess the financial impact to John Hancock resulting from the loss of the Misrepresented Compounds from the nine compound portfolio. These Misrepresented Program Compound analyses are detailed below and in the attached exhibits.

Program Spending Shortfall

21. As part of my analysis in this matter I have also reviewed documents that detail the Program Related Costs as defined and governed by the Agreement. Based on this review, I have determined that at the end of the four-year Program Term, Abbott did not meet its contractual obligations with respect to its expenditures on Program Related Costs.

22. Section 3.3(b) of the Agreement states that:

> *"If Abbott does not spend the Aggregate Carryover Amount on Program Related Costs during such subsequent year[2005], Abbott will pay to John Hancock one-third of the Aggregate Carryover Amount that remains unspent by Abbott, within thirty (30) days after the end of such subsequent year."*[14]

23. A summary of the Program Related Costs and damages resulting from the spending shortfall are shown in Exhibit 6.1. An explanation of the Program Spending Shortfall analysis is found below.

DAMAGES RESULTING FROM THE MISREPRESENTED COMPOUNDS

Methodology

24. My damage analysis relating to the Misrepresented Compounds is detailed in the following paragraphs. To accomplish this analysis, and compute lost royalty payments and lost milestone payments, I have considered the following two scenarios:

- An "*Actual*" scenario representing the current outlook for all nine compounds; and
- a "*But-for*" scenario that assumes that the Misrepresented Compounds were actually as viable as represented by Abbott as of the time of the Agreement.

25. In both scenarios I first computed Expected Sales based on Nominal Sales forecasts and pharmaceutical success rates. I then computed Royalties based on those Expected Sales and the royalty rates set forth in the Agreement. Finally, I computed the expected FDA-approval milestone payments.

[13] All nine Program Compounds were represented by Abbott to be viable compounds in various stages of research and development as of the time of the Agreement.
[14] JH 008078 – 008211, Research Funding Agreement, Article 3.3(b).

26. My computation of lost royalty payments and lost milestone payments is dependant on the Program Compound sales forecasts and the probabilities of regulatory and developmental success. I have chosen to present two scenarios representing a range of damages at this time. First, a more likely Base Case that is based upon Abbott's own expected sales and success rate assumptions; second, an alternative, Low Case that is based upon the lowest available sales and success rate assumptions.[15]

Base Case - Nominal Sales Forecasts

27. In order to compute damages in the Base Case, I first needed to identify appropriate sales forecasts for the "*Actual*" and "*But-for*" scenarios. I considered sales forecasts prepared by both Abbott and John Hancock around the time the Agreement was signed on March 13, 2001, as well as more recent forecasts produced by Abbott in December 2005. The sales forecasts contained nominal sales numbers that assume the drug achieves developmental success and regulatory approval ("Nominal Sales").[16] The Abbott sales documents included projections by Compound and in many cases were broken down by the specific application/indication and geographic sales region for which the Compound was being developed. Commercial assessments and uncertainties surrounding the Compound's market outlook, including information on consumer demand elasticity, the product's life cycle and competing products in the market, are factors cited by Abbott as considerations when developing sales forecasts.[17,18] Deposition testimony of the head of Abbott's Portfolio Analysis Group, Mr. Keith Hendricks, shows that Abbott undertook a thorough process to estimate the potential market for each compound, assuming it achieved FDA approval.[19]

28. For the "*Actual*" scenario I have utilized an estimate of base sales from the most recent sales forecast provided by Abbott. This forecast, dated December 2005, includes projections for the one Program Compound currently in active development by Abbott (ABT-751), and implies a zero sales forecast for the remaining Program Compounds, including the three Misrepresented Compounds.[20] Total Nominal Sales in the "*Actual*" scenario are estimated to equal $974 million (See Exhibit 3.5).

29. For the "*But-for*" scenario I have also utilized an estimate of base sales from the most recent, sales forecast provided by Abbott, as described in the "*Actual*" scenario above, for the active

[15] A range of forecasts have been produced by Abbott, including Low, Base, and Upside sales scenarios. Nominal Sales in the 'but-for' scenario are $10 billion, $20 billion, and $35 billion, respectively. In order to provide a more conservative assessment of damages, I have conducted my analysis based on the Base and Low Sales scenarios only.

[16] I have been unable to determine at this time, based on the documents produced, whether these forecasts represent a full list of regions and applications/indications. If additional information is received, I may further update my report.

[17] ABBT 269161 – 269210.

[18] I have compared the projected development and milestone dates included in the Abbott forecasts to third-party studies, and have found no evidence to suggest that the Abbott assumptions on development timing were unreasonable.

[19] Deposition of Mr. Keith Hendricks, April 27, 2007 (pp. 17-41).

[20] "2006 LRP" sales projections (ABBT 299286-299297). Only the "Expected Commercial" sales forecast was provided, described by Abbott as a combination of the Low, Base and Upside forecast scenarios. Therefore, Nominal Sales utilized in the Base Case have been estimated based on the historical relationship between the Low, Base and Upside forecasts and the "Expected Commercial" forecast on a compound by compound basis.

Program Compound; this is estimated to equal $974 million. In addition, I have included Nominal Sales of $18.7 billion, representing Abbott's "*Global - Base*" forecast for the Misrepresented Compounds as of the time of the Agreement.[21] Nominal Sales in the "*But-for*" scenario therefore equal $19.7 billion. (See Exhibit 3.5).

Base Case - Computation of Expected Sales

30. Because Nominal Sales forecasts do not consider the probabilities that a drug will achieve developmental and regulatory success, I adjusted the Nominal Sales to reflect Expected Sales ("Expected Sales"). This adjustment required assumptions relating to each Compound's probability of success.

31. Many factors and historical experiences are inputs to determining the probability that a compound will achieve developmental and regulatory success. I have compared success rates produced internally by Abbott as well as those from a number of third-party studies, including the DiMasi et al. study (2001) and the CMR International study (2004).[22] For my Base Case analysis, in both the "*Actual*" and "*But-for*" scenarios, I have utilized the success rates developed by Abbott; these success rates are customized for each specific Program Compound and Compound indication and appear to reflect the best, or more-likely, estimate of success as of the date in which the forecasts were produced (See Exhibit 5.1).

32. For the "*Actual*" scenario I have utilized the most recent success rates developed by Abbott for each Program Compound. These success rates, dated December 2005, are rates projected for the Program Compound currently in active development (ABT-751), and imply a zero chance of success for the remaining Program Compounds, including the three Misrepresented Compounds (See Exhibits 5.1 and 5.2). Deposition testimony of Mr. Keith Hendricks shows that Abbott considered multiple sources of information when constructing success rates for compounds in development, and considered its results to be both "realistic" and "reasonable."[23]

33. For the "*But-for*" scenario I have also utilized the most recent success rates developed by Abbott, as described in the "*Actual*" scenario above, for the active Program Compounds. For the Misrepresented Compounds I have utilized success rates developed by Abbott for each Compound as of the time of the Agreement (See Exhibits 5.1 and 5.2).

34. To estimate Expected Sales of the compounds I have multiplied the Nominal Sales shown in Exhibit 3.5 by the success rates detailed in Exhibit 5.2. Based on this approach, Abbott's Expected Sales in the "*But-for*" scenario are approximately $7.9 billion. In the "*Actual*" scenario, without the Misrepresented Compounds, Expected Sales are $399 million (See Exhibit 3.4).[24]

[21] Forecasts provided by Abbott as of the time of the Agreement include the Low, Base, and Upside scenarios; the "Global-Base" scenario has been assumed.
[22] DiMasi, et al, 2001, "*The price of innovation: new estimates of drug development costs.*" See www.cptech.org/ip/health/econ/dimasi2003.pdf; CMR International study of over 1800 new active drugs in development from 1994-2003. See ABBT 308584 – 308645 and ABBT 269161 – 269210
[23] Deposition of Mr. Keith Hendricks, April 27, 2007 (pp. 25, 76).
[24] This process of valuing compounds under development is consistent with, amongst others, the guidelines set forth by the AICPA (see Practice Aid Series, "Assets acquired in a Business Combination to be used in

Base Case - Valuation of John Hancock Lost Royalty Payments

35. Based on the terms of the Agreement and the Expected Sales detailed above, I then computed John Hancock's expected royalty payments for both the "*Actual*" and "*But-for*" scenarios.

36. To do this, I first adjusted Expected Sales detailed in Paragraph 34 in accordance with Article 1.50 of the Agreement that stipulates that John Hancock cannot earn royalties on any one compound for more than 10 years.[25] This adjustment resulted in the reduction of Expected Sales in only the "*But-for*" scenario, from $7.9 billion to $6.1 billion. (See Exhibit 3.2).

37. I then computed royalties based on royalty rates specified in the Agreement that range between 0.5% of net sales and 8.5% of net sales. These rates vary depending on the level of annual net sales aggregated for all nine Program Compounds.[26] Royalties in the "*But-for*" scenario, computed on the $6.1 billion of Expected Sales, equal $424 million (See Exhibit 3.2).

38. I have conducted the same computation of expected royalties in the "*Actual*" scenario where Expected Sales equal $399 million (See Exhibit 3.3). Expected royalties under the "*Actual*" scenario equal $34 million (See Exhibit 3.3).

39. Base Case lost royalty payments to John Hancock relating to the viability of ABT-518, ABT-594, and ABT-773 are then computed as the difference between the expected royalties in the "*But-for*" scenario ($424 million) and the expected royalties in the "*Actual*" scenario ($34 million); the difference is $390 million (See Exhibit 3.1). In present value terms this equals $355 million, not including pre-judgment interest.[27]

Base Case - Valuation of John Hancock Lost Milestone Payments

40. Following the terms of the Agreement, and the projected approval dates and success rates forecast in the "*Actual*" and "*But-for*" scenarios, I have considered the milestone payments John Hancock could have reasonably expected to receive with and without the three Misrepresented Compounds.

41. I first considered the pre-FDA approval milestones, which, according to the Agreement, are capped at $8 million. Because pre-FDA approval milestones have already exceeded this cap, these payments would not be impacted by the developments of the Misrepresented Compounds.[28]

42. I then considered the FDA approval milestones, which, according to the Agreement are capped at $40 million, with $20 million being given to John Hancock for the first approved compound and

Research and Development Activities: A Focus on Software, Electronic Devices, and Pharmaceutical Industries," Chapters 3 and 5) and the FASB (see Statement of Financial Accounting Concepts No. 7). It is also preferred by the United States Office of Management and Budget (see Circular No. A-94).

[25] JH 008078 – 008211, Research Funding Agreement, Article 1.50

[26] JH 008078 – 008211, Research Funding Agreement, Article 7.1

[27] The amount computed therefore reflects the nominal value of past damages plus the present value of future damages estimated as of December 31, 2007. My computation of pre-judgment interest is included in Exhibit 3.1.

[28] JH 008078 – 008211, Research Funding Agreement, Article 6.3

$10 million for each compound thereafter, up to the cap.[29] These milestones, and the years in which the Compounds were projected to achieve FDA approval, are detailed in Exhibit 3.8.

43. Using the payment rules detailed in Paragraph 42, and the Base Case success rates described in paragraphs 32 and 33, I computed Expected Approval Milestones under the "*Actual*" scenario as well as the "*But-for*" scenario (See Exhibits 3.6 and 3.7).[30] On an expected basis, the Program Compounds in the "*But-for*" scenario would yield FDA Approval Milestone payments of $21 million (See Exhibit 3.6). In the "*Actual*" scenario, expected FDA Approval Milestones equal $8 million (See Exhibit 3.7).

44. Base Case lost milestone payments to John Hancock related to the Misrepresented Compounds are then computed as the difference between the expected milestone payments in the "*But-for*" scenario ($21 million) and the expected milestone payments in the "*Actual*" scenario ($8 million); the difference is $13 million (See Exhibit 3.1). In present value terms this equals $13 million, not including pre-judgment interest.[31]

Low Case Overview

45. In addition to the more likely, Base Case, I have considered a Low Case that assumes different Nominal Sales and compound success rates. The same methodology applied in the Base Case analysis detailed above is applied in the Low Case. The following sections describe the Low Case calculation.

Low Case - Nominal Sales Forecasts

46. In reviewing the various sales forecasts detailed in Paragraph 27, I found sales forecasts described as down-side or minimal scenarios. Although these forecasts do not necessarily represent the likely sales potential for the compounds, they do represent lower ranging possible outcomes. For the purpose of computing a Low Case, I have utilized the lowest sales forecast provided.

47. For the *"Actual"* scenario I have utilized an estimate of low sales from the most recent sales forecast provided by Abbott. As in the Base Case, this forecast, dated December 2005, includes projections for the Program Compound currently in active development (ABT-751), and implies a zero sales forecast for the remaining Program Compounds, including the three Misrepresented Program Compounds.[32] Total Nominal Sales in the "*Actual*" scenario are estimated to equal $492 million (See Exhibit 4.5).

[29] JH 008078 – 008211, Research Funding Agreement, Article 6.3
[30] CMR International study of over 1800 new active drugs in development from 1994-2003. See ABBT 308584 – 308645 and ABBT 269161 – 269210
[31] My computation of pre-judgment interest is included in Exhibit 3.1.
[32] "2006 LRP" sales projections (ABBT 299286-299297). Only the 'Expected Commercial' sales forecast was provided, described by Abbott as a combination of the Low, Base and Upside forecast scenarios. Therefore, Nominal Sales utilized in the Low Case have been estimated based on the historical relationship between the Low, Base and Upside forecasts and the 'Expected Commercial' nominal sales forecast on a compound-by-compound basis.

48. For the "*But-for*" scenario I have also utilized an estimate of low sales from the most recent sales forecast provided by Abbott, as described in the "*Actual*" scenario above, for the active Program Compounds; this is estimated to equal $492 million. In addition, I have included Nominal Sales of $9.9 billion, representing Abbott's "*Global - Low*" forecast for the Misrepresented Compounds as of the time of the Agreement.[33] Nominal Sales in the "*But-for*" scenario therefore equal $10.4 billion (See Exhibit 4.5).

Low Case - Computation of Expected Sales

49. As detailed in Paragraph 30, I adjusted the Nominal Sales to reflect Expected Sales based on each Compound's probability of success. For the Low Case, I reviewed a number of Abbott projected and third-party success rates and chose the lowest set of success rates: the CMR International Study (2004)[34]. These success rates, shown in Exhibit 5.1 and detailed in Exhibit 5.3, have been utilized in both the "*Actual*" and "*But-for*" scenarios.

50. To estimate Expected Sales of the compounds in both the "*Actual*" and "*But*-for" scenarios, I have multiplied the Nominal Sales shown in Exhibit 4.5 by the success rates detailed in Exhibit 5.3. Based on this approach, Abbott's Expected Sales in the "*Actual*" scenario are approximately $39 million. In the "*But-for*" scenario, Expected Sales are $3.8 billion (See Exhibit 4.4).

Low Case - Valuation of John Hancock Lost Royalty Payments

51. Based on the terms of the Agreement and the Expected Sales detailed above, I then computed John Hancock's expected royalty payments.

52. To do this, I again adjusted Expected Sales as detailed in Paragraph 36 in accordance with Article 1.50 of the Agreement that stipulates that John Hancock cannot earn royalties on any one compound for more than 10 years. This adjustment resulted in the reduction of Expected Sales in only the "*But-for*" scenario, from $3.8 billion to $2.9 billion. (See Exhibit 4.2).

53. I then computed royalties based on royalty rates specified in the Agreement that range between 0.5% of net sales and 8.5% of net sales. These rates vary depending on the level of annual net sales aggregated for all nine Program Compounds.[35] Royalties in the "*But-for*" scenario, computed on the $2.9 billion of Expected Sales, equal $245 million (See Exhibit 4.2).

54. I have conducted the same computation of expected royalties in the "*Actual*" scenario where Expected Sales equal $39 million (See Exhibit 4.3). Expected royalties under the "*Actual*" scenario equal $3 million (See Exhibit 4.3).

55. Low Case lost royalty payments to John Hancock relating to the viability of ABT-518, ABT-594, and ABT-773 are then computed as the difference between the expected royalties in the "*But-for*" scenario ($245 million) and the expected royalties in the "*Actual*" scenario ($3 million); the

[33] Forecasts provided by Abbott as of the time of the Agreement include the Low, Base, and Upside scenarios; the "Global-Low" scenario has been assumed.
[34] CMR International study of over 1800 new active drugs in development from 1994-2003. See ABBT 308584 – 308645 and ABBT 269161 – 269210.
[35] JH 008078 – 008211, Research Funding Agreement, Article 7.1.

difference is $241 million. (See Exhibit 4.1). In present value terms this equals $221 million, not including pre-judgment interest.[36]

Low Case - Valuation of John Hancock Lost Milestone Payments

56. As described in Paragraphs 40 – 42 for the Base Case, I have considered the terms of the Agreement, the projected approval dates, and success rates forecast in the "Actual" and "But-for" scenarios in order to compute the milestone payments John Hancock could have reasonably expected to receive with and without the three Misrepresented Compounds.

57. Using the payment rules detailed in Paragraph 42, and the Low Case CMR International success rates[37] (See Exhibit 5.3), I computed Expected Approval Milestones under the "*Actual*" scenario as well as the "*But-for*" scenario (See Exhibits 4.6 and 4.7). On an expected basis, the Program Compounds in the "*But-for*" scenario would yield FDA Approval Milestone payments of $18 million (See Exhibit 4.6). In the "*Actual*" scenario, expected FDA Approval Milestones are $2 million (See Exhibit 4.7).

58. Low Case lost milestone payments to John Hancock related to the viability of ABT-518, ABT-594, and ABT-773 are then computed as the difference between the expected milestone payments in the "*But-for*" scenario ($18 million) and the expected milestone payments in the "*Actual*" scenario ($2 million); the difference is $17 million (See Exhibit 4.1). In present value terms this equals $17 million, not including pre-judgment interest.[38]

[36] The amount computed, once again, reflects the nominal value of past damages plus the present value of future damages as of December 31, 2007. My computation of pre-judgment interest is included in Exhibit 4.1.
[37] CMR International study of over 1800 new active drugs in development from 1994-2003. See ABBT 308584 – 308645 and ABBT 269161 – 269210.
[38] Differences are due to rounding. Base Case lost milestone payments are $13.2 million as compared to Low Case lost milestone payments of $16.6 million. My computation of pre-judgment interest is included in Exhibit 4.1.

Lost Royalty and Milestone Summary

59. The following table summarizes my computations of lost royalty and milestone payments in both the Base Case and Low Case scenarios:[39]

Lost Royalty and Lost Milestone Payment Summary
($millions)

Lost Royalty Payment Summary	Base Case[a] ($ millions)	Low Case[b] ($ millions)
But-for Scenario Royalty Payments	424	245
Actual Scenario Royalty Payments	34	3
Lost Royalty Payments - Nominal	390	241
Lost Royalty Payments[c]	355	221

Lost Milestone Payment Summary	Base Case[a] ($ millions)	Low Case[b] ($ millions)
But-for Scenario Milestone Payments	21	18
Actual Scenario Milestone Payments	8	2
Lost Milestone Payments - Nominal	13	17
Lost Milestone Payments[c]	13	17
Total Lost Royalty and Milestone Payments[c],[d]	369	238

(a) See Exhibit 3.1
(b) See Exhibit 4.1
(c) Amount computed reflects the nominal value of past damages plus the present value of future damages, estimated as of December 31, 2007. My computation of pre-judgment interest is included as Exhibit 3.1 and Exhibit 4.1
(d) Total Lost Royalty and Milestone Payments to Hancock have increased from $193m to $221m in the Low Case and $276m to $355m in the Base Case (see Exhibit 2.1).
Differences are due to rounding

[39] The amount computed reflects the nominal value of past damages plus the present value of future damages as of December 31, 2007. My computation of pre-judgment interest is included in Exhibit 3.1 and Exhibit 4.1.

DAMAGES FROM PROGRAM SPENDING SHORTFALL

Methodology and Analysis

60. The Agreement sets Abbott's Aggregate Spending Target at $614 million to be actually spent over the Program Term (2001 – 2004) or as a carryover amount in the subsequent year (2005). Based on documents produced since the filing of my initial report, actual spending during the Program Term was either $442.0 million or $456.2 million, depending on the Abbott document to be relied upon. (See Footnote 4 and Exhibit 6.1).

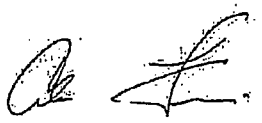
61. Based on actual spending of $456.2 million (as computed from Abbott Laboratories' Amended Responses and Objections to Plaintiff's 2nd Set of Interrogatories) during the Program Term, Abbott generated a $157.8 million shortfall, or Aggregate Carryover Amount, which it was required to spend in the subsequent year. In the subsequent year (2005) Abbott reports spending of $72.9 million, which is $84.9 million short of $157.8 million Aggregate Carryover Amount. (See Exhibit 6.1).

62. According to the Agreement, "*If Abbott does not spend the Aggregate Carryover Amount on Program Related Costs during the subsequent year, Abbott will pay to John Hancock one-third of the Aggregate Carryover Amount that remains unspent by Abbott, within thirty (30) days after the end of such subsequent year.*"[40] Based on a total spending shortfall of $84.8 million, I have computed this one-third spending shortfall damage amount owed to John Hancock to equal $28.3 million, not including pre-judgment interest.[41] (See Exhibit 6.1).

63. Using the same methodology, and based on actual spending amount of $442 million (as computed from the 2008 Annual Research Plan) I have computed the one-third spending shortfall damage amount owed to John Hancock to equal $33.0 million, not including pre-judgment interest. (See Footnote 41 and Exhibit 6.1).

The foregoing report represents my opinions in this matter.

Respectfully submitted:



Alan Friedman

[40] JH 008078 - 008211, Research Funding Agreement, Section 3.3(b).
[41] My computation of pre-judgment interest is included in Exhibit 6.1

CRA INTERNATIONAL

ALAN FRIEDMAN, CMC

Vice President

M:B.A. Finance,
Northeastern University

B.A. Economics and Business,
Lafayette College

Post-Graduate Course Work
University of Chicago,
Graduate School of Business

Alan Friedman has 25 years of financial consulting experience and has provided expert testimony on the subject of damages in numerous intellectual property cases and complex commercial litigations. He has consulted on mergers and acquisitions, financings, operations improvement, valuations, and claims for economic loss. He has led teams of professionals to arrange and evaluate transactions ranging from $3 million to $3 billion.

In intellectual property litigation matters, Mr. Friedman has been retained to compute damages in patent infringement, software copyright infringement, and trade secret cases, including one which resulted in one of the largest copyright infringement awards ever given. In complex commercial litigations, he has been retained to testify on damages in matters involving breach of contract, acquisitions, financings, mutual fund investing, and employee termination. He has testified in federal and state court, as well as in arbitrations and mediations.

He has accomplished assignments for private and publicly-owned companies, both domestic and foreign. The industry groups in which those companies operate include medical products, manufacturing, business services, retail, computer hardware and software, consumer products, apparel, and financial services.

Mr. Friedman founded and served as President of a 14-man boutique consulting and investment banking firm which advised in the areas of acquisition analysis and structuring, financing, strategic and tactical planning, and damage analysis and expert testimony.

Prior to that, Mr. Friedman worked for Deloitte & Touche as a Consulting Partner and Staff Member, held leadership positions in the National Financial Consulting and Litigation Consulting Groups, and chaired its Financial Modeling Task Force.

Mr. Friedman also worked for the Continental Group, Inc., in its U.S. and International Packaging Divisions and its Corporate Office in the areas of finance, acquisitions, business development financial systems, and new product evaluation.

Exhibit 1.2
Recent Testimony Experience of Alan Friedman

- Genentech, Inc. v. **Boerhinger Mannheim, Gmbh and Boerhinger Mannheim Corporation** (District of Massachusetts)
  Deposition

- Gen-Probe Incorporated v. **Bayer Corporation** (JAMS arbitration)
  Deposition and Hearing Testimony

- Medtronic Inc. v. **Boston Scientific Inc.** (District of Minnesota)
  Deposition and Testimony at Trial

- James Clouser v. **Ion Beam Applications, Inc.** (American Arbitration Association)
  Hearing Testimony

- **Earnings Performance Group, Inc.** v. Robert L. Quigley, Jr., Eugene Carrigan, and Bank Insight, LLC (Eastern District of Michigan)
  Deposition Testimony

- **Earnings Performance Group, Inc.** v. Carreker-Antinori, Inc. (District of New Jersey)
  Deposition and Trial Testimony

- **Boston Scientific Scimed Inc. and Boston Scientific Corporation** v. Cordis Corporation and Johnson and Johnson, Inc.
  Deposition Testimony

- **Brian Whitney** v. USI Consulting Group, Inc., USI Holdings Corporation and USI Insurance Services Corp. (American Arbitration Association)
  Deposition and Hearing Testimony

Exhibit 1.3
Documents Considered

Produced Documents

ABBT	0000038	- 0003445	JH	002078	- 002344	JH	005147	- 005611
ABBT	0003457	- 0004028	JH	002347	- 002350	JH	006001	- 006649
ABBT	0004031	- 0004338	JH	002359	- 002371	JH	006707	- 006786
ABBT	0004340	- 0027339	JH	002373	- 002390	JH	006801	- 006807
ABBT	0027416	- 0033144	JH	002393	- 002409	JH	006882	- 006934
ABBT	0033178	- 0040628	JH	002412	- 002420	JH	007032	- 007144
ABBT	100001	- 126938	JH	002423	- 002444	JH	007185	- 007357
ABBT	127043	- 196502	JH	002447	- 002644	JH	007363	- 007373
ABBT	200001	- 372705	JH	002659	- 002661	JH	007382	- 007384
AL	000001	- 000572	JH	002673	- 002782	JH	007391	- 007393
AL	000649	- 000661	JH	002970	- 003103	JH	007400	- 007411
AL	000665	- 000666	JH	003107	- 003111	JH	007417	- 007419
AL	000743	- 000743	JH	003113	- 003158	JH	007425	- 007427
AL	000748	- 000748	JH	003160	- 003348	JH	007431	- 007456
AL	000790	- 000790	JH	003350	- 003460	JH	007492	- 007844
AL	000837	- 000837	JH	003493	- 003534	JH	007848	- 008047
AL	000884	- 000886	JH	003537	- 003540	JH	008063	- 008212
AL	000983	- 001557	JH	003544	- 003547	JH	008234	- 008439
AL	001560	- 001814	JH	003551	- 003563	JH	008441	- 008443
AL	001816	- 002022	JH	003611	- 003617	JH	008451	- 008931
AL	002026	- 002076	JH	003651	- 003873	JH	009438	- 009507
JH	000065	- 000761	JH	003931	- 004462	JH	009566	- 009673
JH	000772	- 001361	JH	004481	- 004704	JH	009675	- 010493
JH	001363	- 001499	JH	004780	- 004812	MCK	000023	- 000026
JH	001502	- 001759	JH	004911	- 004918	MCK	00488	- 00488
JH	001762	- 002073	JH	004976	- 005011	MCK	000537	- 000537

Legal Filings

	Filing Date	CA#
Complaint: John Hancock Life Insurance Company v. Abbott Laboratories	6/3/2005	05-11150-DPW
Supplemental Complaint: John Hancock Life Insurance Company v. Abbott Laboratories	6/23/2006	05-11150-DPW
John Hancock Life Insurance v. Abbott Laboratories	9/16/2005	03-12501-DPW
Defendant's responses and objections to plaintiffs' second set of interrogatories	6/30/2006	05-11150-DPW
First Amended Supplemental Complaint	12/29/2006	05-11150-DPW
Plaintiff John Hancock's Responses and Objections to Defendant Abbot Laboratories' Third Set of Interrogatories	4/30/2007	05-11150-DPW
Abbott Laboratories' Amended Responses and Objections to Plaintiffs' Second Set of Interrogatories	8/3/2007	05-11150-DPW
Abbott's Memorandum in Support of Motion in Limine to Exclude Testimony of Mr. Alan Friedman	10/12/2007	05-11150-DPW
Plaintiffs' Memorandum in Opposition to Defendant's Motion in Limine to Exclue Expert Testimony of Mr. Alan Friedmen	10/19/2007	05-11150-DPW

Depositions

Paul Andrews, Stephen Blewitt, Stanley Bukofzer, Michelle Cambell, Stephen Cohen, Marilyn Collicot, Deirdre Daesen, Diane D'Amico, Wilma Davis, Philip Deemer, William Fairweather, Jeanne Fox, Barry Gold, Mark Hair, Scott Hartz, Keith Hendricks, Jessica Hopfield, Ellen Klaus, Lynn Klotz, Elizabeth Kowaluk, Andrea Landsberg, William Lee, Jeffrey Leiden, John Leonard, Lisa Loberg, James Looman, Frank Loughery, Thomas Lyons, Christopher Martinez, John Mastromarino, Bruce McCarthy, Carol Meyer, Michael Meyer, Azmi Nabulsi, Roger Natsou, Perry Nisen, Daphne Pals, Bruce Rodda, Christopher Silber, Brian Smith, James Thomas, Kevin Tormey, Avram Tucker, Shannon Walsh, Amy Weed, Barry Welch, Thomas Woidat

Other Sources

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AICPA Practice Aid Series, "Assets Acquired in a Business Combination to Be Used in Research and Development Activities: A Focus on Software, Electronic Devices, and Pharmaceutical Industries. Chap. 5 (2001).

Exhibit 1.3
Documents Considered

Produced Documents

ABBT 0000038	- 0003445	JH 002078	- 002344	JH	005147	- 005611
ABBT 0003457	- 0004028	JH 002347	- 002350	JH	006001	- 006649

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Research Funding Agreement Update (November 20, 2007)
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www.abbott.com
www.pharmapredict.com
www.ustreas.gov/offices/domestic-finance/debt-management/interest-rate/yield_historical.shtml

Exhibit 2.1
Summary[1]
($millions)

Damages Related to Misrepresented Compounds[5]	BASE CASE Damages ($millions)[2]	LOW CASE Damages ($millions)[3]
Lost Royalty Payments	355	221
Lost Milestone Payments	13	17
Total	369	238

Aggregate Spending Shortfall	Damages ($millions)
Spending Shortfall Damages[4][6]	28.3

Note:

(1) The present value computed reflects the past actual value and and the future present value of damages as of December 31, 2007. See Exhibits 3.1, 3.2 and 6.1 for my computation of pre-judgment interest.
(2) See Exhibit 3.1.
(3) See Exhibit 4.1.
(4) See Exhibit 6.1.
(5) Total Damages to Hancock have increased from $193m (initial report) to $238m (12/3/2007 updated report) in the Low Case and $276m (initial report) to $369m (12/3/2007 updated report) in the Base Case (see Exhibits 3.1 and 4.1).
(6) Spending Shortfall Damages have increased from 21.8m (initial report) to 28.3m (12/3/2007 updated report) (see Exhibit 6.1).
Differences are due to rounding

Exhibit 3.1
BASE CASE
Lost Payment Computation
($millions)

Item	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals
Expected Royalty Payments (But-for Scenario)[1]	1	12	23	35	41	47	50	51	50	51	34	17	12	424
Expected Royalty Payments (Actual Scenario)[2]	-	-	-	-	-	-	0	1	1	4	9	11	7	34
Lost Royalty Payments - Nominal	1	12	23	35	41	47	50	50	49	47	25	5	5	390
Present Value Factor for Future Damages (Discount Rate = 4.04%)[3]	1	1	1	1	1.00	0.96	0.92	0.89	0.85	0.82	0.79	0.76	0.73	
Present Value of Lost Royalty Payments[4],[5],[9]	1	12	23	35	41	45	46	44	42	38	20	4	4	355
Cumulative Payments (Principal plus Interest)	1.0	13.1	37.1	74.0	118.7									
Pre-judgment Interest[11]		0.1	0.7	1.9	3.7	-	-	-	-	-	-	-	-	6.3

Item	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals
Expected Milestone Payments (But-for Scenario)[6]	-	16	-	1	-	-	4	-	-	-	-	-	-	21
Expected Milestone Payments (Actual Scenario)[7]	-	-	-	-	-	-	8	-	-	-	-	-	-	8
Lost Milestone Payments - Nominal	-	16	-	1	-	-	(4)	-	-	-	-	-	-	13
Present Value Factor for Future Damages (Discount Rate = 4.04%)[3]	1	1	1	1	1.00	0.96	0.92	0.89	0.85	0.82	0.79	0.76	0.73	
Present Value of Lost Milestone Payments[7],[8],[10]	-	16	-	1	-	-	(4)	-	-	-	-	-	-	13
Cumulative Payments (Principal plus Interest)	-	16.0	16.8	18.9	19.8									
Pre-judgment Interest[11]		-	0.8	0.8	0.9	-	-	-	-	-	-	-	-	2.6

Notes:
(1) See Exhibit 3.2
(2) See Exhibit 3.3
(3) (1 yr Treasury Rate as of 10/31/2007) http://www.ustreas.gov/offices/domestic-finance/debt-management/interest-rate/yield_historical.shtml
(4) The amount computed reflects the nominal value of past damages and the present value of future damages as of December 31, 2007.
(5) Lost Royalty Payments X Present Value Factor.
(6) See Exhibit 3.6
(7) See Exhibit 3.7
(8) Lost Milestone Payments X Present Value Factor.
(9) Lost Royalty Payments to Hancock have increased from $262m (initial report) to $355m (12/3/2007 updated report) due to the tiered royalty structure.
(10) Lost Milestone Payments have decreased from $14m (initial report) to $13m (12/3/2007 updated report) due to the termination of ABT-510 and ABT-627 (see Exhibits 3.6-3.8).

(11) Under Illinois law the statutory rate of 5% is available on damages resulting from a breach of contract. See 815 ILCS Sec. 205/2 ; Transportation & Train Assoc. v. Morrison Knudsen Corp., 225 F.3d 397 (7th Cir. 2001). The same is true for cases arising in equity . See In re Estate v. Wernick, 535 N.E. 2d 876 (Ill. S.Ct. 1989). We have assumed the 5% statutory rate as a reasonable rate of pre-judgment interest.
Differences are due to rounding

Exhibit 3.2
BASE CASE
Expected Hancock Royalty Computation - "But-for" Scenario[1][4]
($millions)

Category	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals
Expected Sales[1]	12	141	274	427	574	719	798	815	811	824	859	863	764	7,882
Reduction for 10-Year Royalty Limit[2]	-	-	-	-	-	-	-	-	-	-	451	667	625	1,744
Expected Sales after Reduction	12	141	274	427	574	719	798	815	811	824	408	195	139	6,138
8.5% of Yearly Net Sales up to $400M[3]	1	12	23	34	34	34	34	34	34	34	34	17	12	337
4.0% of Yearly Net Sales in excess of $400M up to $1B[3]	-	-	-	1	7	13	16	17	16	17	0	-	-	87
1.0% of Yearly Net Sales in excess of $1B up to $2B[3]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
0.5% of Yearly Net Sales in excess of $2B[3]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Expected Royalty Payments	1	12	23	35	41	47	50	51	50	51	34	17	12	424

Note:
(1) See Exhibit 3.4. "But-for" Scenario assumes projections as of the Agreement for Misrepresented Compounds plus the most current outlook for the six Other Program Compounds.
(2) 10 year Royalty Term limit for each Program Compound (see JH 008078 - 008211, Article 1.50). Therefore, the following adjustments have been made: Annual Expected Net Sales were reduced for the following Compounds: ABT-594 (Expected Net Sales for 2014-2015 eliminated) and ABT-773 (Expected Net Sales for 2013-2015 eliminated).
(3) See JH 008078 - 008211 (Articles 7.1 and 7.2).
(4) Expected Royalty Payments to Hancock have decreased from $546m (initial report) to $424m (12/3/2007 updated report) due to the decreased expected sales forecast (see Exhibit 3.4).
Differences are due to rounding

Exhibit 3.3
BASE CASE
Expected Hancock Royalty Computation - "Actual" Scenario[1][4]
($millions)

Category	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals
Expected Sales[1]	-	-	-	-	-	-	3	9	17	51	107	135	77	399
Reduction for 10-Year Royalty Limit[2]	-	-	-	-	-	-	-	-	-	-	-	-	-	
Expected Sales after Reduction	-	-	-	-	-	-	3	9	17	51	107	135	77	399
8.5% of Yearly Net Sales up to $400M[3]	-	-	-	-	-	-	0	1	1	4	9	11	7	34
4.0% of Yearly Net Sales in excess of $400M up to $1B[3]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1.0% of Yearly Net Sales in excess of $1B up to $2B[3]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
0.5% of Yearly Net Sales in excess of $2B[3]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Expected Royalty Payments	-	-	-	-	-	-	0	1	1	4	9	11	7	34

Note:
(1) See Exhibit 3.4. "Actual" Scenario assumes the most current outlook for the nine Program Compounds, inlcuding a zero sales forecast for the Misrepresented Compounds.
(2) 10 year Royalty Term limit for each Program Compound (see JH 008078 - 008211, Article 1.50). Based on the most current scenario, Annual Expected Net Sales reach the 2015 Agreement Termination date before the 10 year Royalty Term limit is reached for all Program Compounds. Therefore, no adjustments have been made.
(3) See JH 008078 - 008211 (Articles 7.1 and 7.2).
(4) Expected Royalty Payments to Hancock have decreased from $250m (initial report) to $34m (12/3/2007 updated report) due to the decreased expected sales forecast (see Exhibit 3.4).
Differences are due to rounding

Exhibit 3.4
BASE CASE
Expected Net Sales Forecast by Program Compound, Indication, and Geographic Region [1][2]
($millions)

Program Compound	Indication	Region	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals
Misrepresented Program Compounds (As of Agreement Date: March 13, 2001)																
ABT-518	All	Global	-	-	-	3	8	15	26	34	48	53	59	61	62	368
ABT-594	Chron. Pere. Pain	Global	-	2	6	11	18	25	32	33	32	30	29	29	27	274
ABT-594	Neuro Pain	Global	-	10	43	84	124	167	209	218	215	213	210	207	198	1,898
ABT-594	Nociceptive Pain	Global	-	-	0.3	1	1	2	2	2	3	3	3	3	2	21
ABT-773	Tablet	Global	12	130	212	296	376	446	449	436	417	397	377	356	337	4,239
ABT-773	IV	Global	-	-	9	19	27	36	44	48	48	46	45	45	34	401
ABT-773	Japan	Global	-	-	5	12	19	29	33	33	33	31	30	28	27	280
Subtotal			*12*	*141*	*274*	*427*	*574*	*719*	*795*	*806*	*794*	*773*	*752*	*728*	*687*	*7,483*
Other Program Compounds (As of Most Recent Documentation: December 2005)																
ABT-510	Non-Sarcoma	US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-510	Non-Sarcoma	Ex-US	-	-	-	-	-	-	2	3	7	19	34	42	24	131
ABT-751	All	US	-	-	-	-	-	-	1	6	10	33	73	93	53	269
ABT-751	All	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Non PCA	US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Non PCA	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	HRPCA	US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	HRPCA	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Japan	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Ph IV Studies	US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Ph IV Studies	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-100	All	Global	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-724	All	Global	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-492	All	Global	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Subtotal (Actual Scenario)			-	-	-	-	-	-	*3*	*9*	*17*	*51*	*107*	*135*	*77*	*399*
Expected Net Sales (But-for Scenario)			12	141	274	427	574	719	798	815	811	824	859	863	764	7,882

Note:
(1) Nominal sales forecast X projected success rates (see Exhibit 3.5 and 5.1).
(2) Expected net sales have decreased from $3.3 billion (initial report) to $399m (12/3/2007 updated report) in the Actual Scenario and from $10.8 billion (initial report) to $7.9 billion (12/3/2007 updated report) in the But-for Scenario, based on the removal of projected sales for ABT-510 and ABT-627 (see Exhibit 3.5).
Differences are due to rounding

Exhibit 3.5
BASE CASE
Nominal Net Sales Forecast by Program Compound, Indication, and Geographic Region[10]
($millions)

Program Compound	Indication	Region	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals
Misrepresented Program Compounds (As of Agreement Date: March 13, 2003) [1]																
ABT-518[2]	All	Global	-	-	-	22	67	116	210	274	382	425	468	485	496	2,945
ABT-594[3]	Chron. Perc. Pain	Global	-	13	36	70	111	159	200	206	197	189	184	180	169	1,714
ABT-594[3]	Neuro Pain	Global	-	31	135	268	395	531	665	692	683	675	666	657	628	6,026
ABT-594[3]	Nociceptive Pain	Global	-	-	4	9	16	22	29	33	35	35	35	34	33	285
ABT-773[7]	Tablet	Global	17	180	294	411	522	619	623	606	579	551	523	495	468	5,888
ABT-773[7]	IV	Global	-	-	25	54	76	99	121	134	133	129	126	124	94	1,115
ABT-773[7]	Japan	Global	-	-	13	33	52	77	89	89	87	83	79	75	71	748
Subtotal			*17*	*224*	*507*	*867*	*1,239*	*1,623*	*1,937*	*2,034*	*2,096*	*2,087*	*2,081*	*2,050*	*1,959*	*18,721*
Other Program Compounds (As of Most Recent Documentation: December 2005) [1]																
ABT-510	Non-Sarcoma	US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-510	Non-Sarcoma	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-751	All	US[9]	-	-	-	-	-	-	4	8	18	45	84	102	59	320
ABT-751	All	Ex-US[9]	-	-	-	-	-	-	3	14	23	80	178	227	129	654
ABT-627	Non PCA	US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Non PCA	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	HRPCA	US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	HRPCA	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Japan	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Ph IV Studies	US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Ph IV Studies	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-100	All	Global	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-724	All	Global	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-492	All	Global	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Subtotal (Actual Scenario)			-	-	-	-	-	-	*7*	*22*	*41*	*125*	*262*	*329*	*188*	*974*
Nominal Net Sales (But-for Scenario)			17	224	507	867	1,239	1,623	1,944	2,056	2,137	2,212	2,343	2,379	2,147	19,695

Notes:
(1) Nominal Net Sales forecasts for Non-viable Program Compounds taken from Abbott "Total Base" sales projections.

(2) Nominal Net Sales forecasts from "2006 LRP" sales projections (ABBT 299286-299297 and ABBT 299147-299158). Only the "Expected Commercial" sales forecast was provided, described by Abbott as a combination of the Low, Base and Upside scenarios. Therefore, Nominal Sales utilized in the Base Case have been estimated based on the historical relationship between the Low, Base and Upside forecasts and the "Expected Commercial" forecast on a compound by compound basis.
(3) See ABBT 0003362 - 0003364.
(4) See ABBT 0003365 - 0003367.
(5) See ABBT 0003368 - 0001170.
(6) See ABBT 0003416 - 003418.
(7) See ABBT 329442 - 329558 .
(8) See ABBT 299286 - 299297.
(9) See ABBT 299147 - 299158.
(10) Nominal Net Sales have decreased from $11.3 billion (initial report) to $974m (12/3/2007 updated report) in the Actual Scenario, and in effect have decreased from $30.0 billion (initial report) to $19.7 billion (12/3/2007 updated report) in the But-for Scenario, based loss of projected sales for ABT-510 and ABT-627 due to their recent terminations. Although ABT-751 is still being developed, its forecasted nominal sales reflect its status as of December 2005.
Differences are due to rounding

Exhibit 3.6
BASE CASE
Expected Hancock Milestones by Compound - "But-for" Scenario[1][3]
($millions)

Program Compound	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals[1]
Misrepresented Program Compounds (As of Agreement Date: March 13, 2001)														
ABT-518	-	-	-	1	-	-	-	-	-	-	-	-	-	1
ABT-594	-	2	-	-	-	-	-	-	-	-	-	-	-	2
ABT-773	-	14	-	-	-	-	-	-	-	-	-	-	-	14
Subtotal	-	*16*	-	*1*	-	-	-	-	-	-	-	-	-	*17*
Other Program Compounds (As of Most Recent Documentation: December 2005)														
ABT-510	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-751	-	-	-	-	-	-	4	-	-	-	-	-	-	4
ABT-627	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-100	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-724	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-492	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Subtotal	-	-	-	-	-	-	*4*	-	-	-	-	-	-	*4*
Expected Hancock Milestones	-	16	-	1	-	-	4	-	-	-	-	-	-	21

Note:
(1) Nominal milestone forecast X projected success rates (see Exhibit 3.8 and 5.1). Success rate for Compound Indication with the highest probability of launch applied to the corresponding Nominal Projected Milestone Payment for each Compound.
(2) Aggregate Milestone Payment Cap: $40M (see JH 008078 - 008211, Article 6).
(3) Expected Milestone Payments to Hancock have decreased from $26m (initial report) to $21m (12/3/2007 updated report) due to decreased Nominal Milestone Payments (see Exhibit 3.8).
Differences are due to rounding

Exhibit 3.7
BASE CASE
Expected Hancock Milestones by Compound - "Actual" Scenario[1][5]
($millions)

Program Compound	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals[2]
Misrepresnted Program Compounds (As of Agreement Date: March 13, 2001) [3]														
ABT-518	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-594	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-773	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Subtotal	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other Program Compounds (As of Most Recent Documentation: December 2005)														
ABT-510	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-751[4]	-	-	-	-	-	-	8	-	-	-	-	-	-	8
ABT-627	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-100	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-724	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-492	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Subtotal	-	-	-	-	-	-	*8*	-	-	-	-	-	-	*8*
Expected Hancock Milestones	-	-	-	-	-	-	8	-	-	-	-	-	-	8

Note:
(1) Nominal milestone forecast X projected success rates (see Exhibit 3.8 and 5.1). Success rate for Compound Indication with the highest probability of launch applied to the corresponding Nominal Projected Milestone Payment for each Compound.
(2) Aggregate Milestone Payment Cap: $40 million (see JH 008078 - 008211, Article 6).
(3) Misrepresented Program Compounds have an assumed 0% success rate.
(4) Nominal Milestone payment forecast for ABT-751 is $20 million. ABT-751 expected to be the first Program Compound to receive FDA Approval.
(5) Expected Milestone Payments to Hancock have decreased from $12m (intital report) to $8m (12/3/2007 updated report) based on the decreased Nominal Milestone Payments (see Exhibit 3.8).
Differences are due to rounding

Exhibit 3.8

Nominal FDA Approval Milestone Payment Forecast by Program Compound

($millions)

Program Compound	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals
Misrepresented Program Compounds (As of Agreement Date: March 13, 2001)														
ABT-518	-	-	-	10	-	-	-	-	-	-	-	-	-	10
ABT-594	-	10	-	-	-	-	-	-	-	-	-	-	-	10
ABT-773	-	20[1]	-	-	-	-	-	-	-	-	-	-	-	20
Subtotal	-	*30*	-	*10*	-	-	-	-	-	-	-	-	-	40
Other Program Compounds (As of Most Recent Documentation: December 2005) [3]														
ABT-510	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-751	-	-	-	-	-	-	20[2]	-	-	-	-	-	-	20
ABT-627	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-100	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-724	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-492	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Subtotal	-	-	-	-	-	-	*20*	-	-	-	-	-	-	*20*
Nominal Net Milestones	-	30	-	10	-	-	20		-	-	-	-	-	60

Note:

(1) Assuming all Program Compounds were viable ("But-for" scenario), ABT-773 was expected to be the first Program Compound to receive FDA Approval (see JH 008133 - JH 008132). $20 million milestone payment applies to first approval. $10 milestone payment applies to subsequent approvals.

(2) Assuming Progam Compunds ABT-518, ABT-594, and ABT-773 were Non-viable ("Actual" scenario), ABT-751 is expected to be the first Program Compound to receive FDA Approval. $20 million milestone payment applies to first approval. $10 million milestone payment applies to subsequent approvals.

(3) Status of the Other Program Compounds has been updated to reflect the status quo as of 12/3/2007; therefore, forecasted nominal milestone payments for ABT-510 and ABT-627 have been reduced to 0 due to recent terminations. Although ABT-751 is still being developed, its projected launch date reflects its status as of December 2005.

Differences are due to rounding

Exhibit 4.1
LOW CASE
Lost Payment Computation
($millions)

Item	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals
Expected Royalty Payments (But-for Scenario)[1]	1	7	14	19	26	32	34	34	34	33	8	2	2	245
Expected Royalty Payments (Actual Scenario)[2]	-	-	-	-	-	-	0	0	0	0	1	1	1	3
Lost Royalty Payments - Nominal	1	7	14	19	26	32	34	34	33	32	7	1	1	241
Present Value Factor for Future Damages (Discount Rate = 4.04%)[3]	1	1	1	1	1.00	0.96	0.92	0.89	0.85	0.82	0.79	0.76	0.73	
Present Value of Lost Royalty Payments[4],[5],[9]	1	7	14	19	26	31	31	30	29	26	6	1	1	221
Cumulative Payments (Principal plus Interest)	0.6	7.6	21.7	42.2	70.0									3.6
Pre-judgment Interest[11]		0.0	0.4	1.1	2.1	-	-	-	-	-	-	-	-	

Item	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals
Expected Milestone Payments (But-for Scenario)[6]	-	17	-	1	-	-	1	-	-	-	-	-	-	18
Expected Milestone Payments (Actual Scenario)[7]	-	-	-	-	-	-	2	-	-	-	-	-	-	2
Lost Milestone Payments - Nominal	-	17	-	1	-	-	(1)	-	-	-	-	-	-	17
Present Value Factor for Future Damages (Discount Rate = 4.04%)[3]	1	1	1	1	1.00	0.96	0.92	0.89	0.85	0.82	0.79	0.76	0.73	
Present Value of Lost Milestone Payments[4],[8],[10]	-	17	-	1	-	-	(1)	-	-	-	-	-	-	17
Cumulative Payments (Principal plus Interest)	-	16.7	17.6	19.1	20.0									2.7
Pre-judgment Interest[11]		-	0.8	0.9	1.0	-	-	-	-	-	-	-	-	

Note:
(1) See Exhibit 4.2
(2) See Exhibit 4.3
(3) (1 yr Treasury Rate as of 10/31/2007) http://www.ustreas.gov/offices/domestic-finance/debt-management/interest-rate/yield_historical.shtml
(4) The amount computed reflects the nominal value of past damages and the present value of future damages as of December 31, 2007.
(5) Lost Royalty Revenue X Present Value Factor.
(6) See Exhibit 4.6
(7) See Exhibit 4.7
(8) Lost Milestone Payments X Present Value Factor.
(9) Lost Royalty Payments to Hancock have increased from $180m (initial report) to $221m (12/3/2007 updated report) due to the tiered royalty structure.
(10) Lost Milestone Payments have increased from $14m (initial report) to $17m (12/3/2007 updated report) due to the termination of ABT-510 and ABT-627 (see Exhibits 4.6-4.8).
(11) Under Illinois law the statutory rate of 5% is available on damages resulting from a breach of contract. See 815 ILCS Sec. 205/2; Transportation & Train Assoc. v. Morrison Knudsen Corp., 225 F.3d 397 (7th Cir. 2001). The same is true for cases arising in equity. See In re Estate v. Wernick, 535 N.E. 2d 876 (Ill. S.Ct. 1989). We have assumed the 5% statutory rate as a reasonable rate of pre-judgment interest.
Differences are due to rounding

Exhibit 4.2
LOW CASE
Expected Hancock Royalty Computation - "But-for" Scenario[1][4]
($millions)

Category	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals
Expected Sales[1]	7	82	162	227	303	374	399	403	396	385	377	365	339	3,818
Reduction for 10-Year Royalty Limit[2]	-	-	-	-	-	-	-	-	-	-	280	339	319	938
Expected Sales after Reduction	7	82	162	227	303	374	399	403	396	385	96	26	20	2,880
8.5% of Yearly Net Sales up to $400M[3]	1	7	14	19	26	32	34	34	34	33	8	2	2	245
4.0% of Yearly Net Sales in excess of $400M up to $1B[3]	-	-	-	-	-	-	-	0.1	-	-	-	-	-	0.1
1.0% of Yearly Net Sales in excess of $1B up to $2B[3]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
0.5% of Yearly Net Sales in excess of $2B[3]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Expected Royalty Payments	1	7	14	19	26	32	34	34	34	33	8	2	2	245

Note:
(1) See Exhibit 4.4. "But-for" Scenario assumes projections as of the Agreement for the Misrepresented Compounds plus the most current outlook for the six Other Program Compounds.
(2) 10 year Royalty Term limit for each Program Compound (see JH 008078 - 008211, Article 1.50). Therefore, the following adjustments have been made: Annual Expected Net Sales were reduced for the following Compounds: ABT-594 (Expected Net Sales for 2014-2015 eliminated) and ABT-773 (Expected Net Sales for 2013-2015 eliminated).
(3) See JH 008078 - 008211 (Articles 7.1 and 7.2).
(4) Expected Royalty Payments to Hancock have decreased from $356m (initial report) to $245m (12/3/2007 updated report) due to the decreased expected sales forecast (see Exhibit 4.4).
Differences are due to rounding

Exhibit 4.3
LOW CASE
Expected Hancock Royalty Computation - "Actual" Scenario[1][4]
($millions)

Category	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals
Expected Sales[1]	-	-	-	-	-	-	0	1	2	5	11	13	8	39
Reduction for 10-Year Royalty Limit[2]	-	-	-	-	-	-	-	-	-	-	-	-	-	
Expected Sales after Reduction	-	-	-	-	-	-	0	1	2	5	11	13	8	39
8.5% of Yearly Net Sales up to $400M[3]	-	-	-	-	-	-	0	0	0	0	1	1	1	3
4.0% of Yearly Net Sales in excess of $400M up to $1B[3]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1.0% of Yearly Net Sales in excess of $1B up to $2B[3]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
0.5% of Yearly Net Sales in excess of $2B[3]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Expected Royalty Payments	-	-	-	-	-	-	0	0	0	0	1	1	1	3

Note:
(1) See Exhibit 4.4. "Actual" Scenario assumes the most current outlook for the nine Program Compounds, inlcuding a zero sales forecast for the Misrepresented Compounds.
(2) 10 year Royalty Term limit for each Program Compound (see JH 008078 - 008211, Article 1.50). Based on the most current scenario, Annual Expected Net Sales reach the 2015 Agreement Termination date before the 10 year Royalty Term limit is reached for all Program Compounds. Therefore, no adjustments have been made.
(3) See JH 008078 - 008211 (Articles 7.1 and 7.2).
(4) Expected Royalty Payments to Hancock have decreased from $151m (initial report) to $3m (12/3/2007 updated report) due to the decreased expected sales forecast (see Exhibit 4.4).
Differences are due to rounding

Exhibit 4.4
LOW CASE
Expected Net Sales Forecast by Program Compound, Indication, and Geographic Region[1][2]
($millions)

Program Compound	Indication	Region	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals
Misrepresented Program Compounds (As of Agreement Date: March 13, 2001)																
ABT-518	All	Global	-	-	-	0.2	1	2	4	6	10	11	12	12	12	72
ABT-594	Chron. Pere. Pain	Global	-	2	6	12	19	27	34	35	33	32	31	31	29	291
ABT-594	Neuro Pain	Global	-	4	17	12	21	29	36	37	38	37	36	35	33	335
ABT-594	Nociceptive Pain	Global	-	-	1	2	3	4	5	6	6	6	6	6	6	48
ABT-773	Tablet	Global	7	77	129	181	230	272	274	269	258	246	235	223	213	2,614
ABT-773	IV	Global	-	-	6	13	18	23	27	29	29	28	28	27	22	246
ABT-773	Japan	Global	-	-	3	8	12	18	20	20	20	19	18	18	17	172
Subtotal			*7*	*82*	*162*	*227*	*303*	*374*	*399*	*403*	*394*	*380*	*366*	*351*	*331*	*3,779*
Other Program Compounds (As of Most Recent Documentation: December 2005)																
ABT-510	Non-Sarcoma	US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-510	Non-Sarcoma	Ex-US	-	-	-	-	-	-	0.2	0.3	1	2	3	4	2	13
ABT-751	All	US	-	-	-	-	-	-	0.1	1	1	3	7	9	5	26
ABT-751	All	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Non PCA	US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Non PCA	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	HRPCA	US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	HRPCA	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Japan	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Ph IV Studies	US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Ph IV Studies	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-100	All	Global	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-724	All	Global	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-492	All	Global	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Subtotal (Actual Scenario)			-	-	-	-	-	-	*0*	*1*	*2*	*5*	*11*	*13*	*8*	*39*
Expected Net Sales (But-for Scenario)			7	82	162	227	303	374	399	403	396	385	377	365	339	3,818

Note:
(1) Nominal sales forecast X projected success rates (see Exhibit 4.5 and 5.1).
(2) Expected net sales have decreased from $1.8 billion (initial report) to $39m (12/3/2007 updated report) in the Actual Scenario, and in effect have decreased from $3.6 billion (initial report) to $3.8 billion (12/3/2007 updated report) in the But-for Scenario, based on the removal of projected sales for ABT-510 and ABT-627 (see Exhibit 4.5).
Differences are due to rounding

Exhibit 4.5
LOW CASE
Nominal Net Sales Forecast by Program Compound, Indication, and Geographic Region[11]
($millions)

Program Compound	Indication	Region	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals
Misrepresented Program Compounds (As of Agreement Date: March 13, 2001)[7]																
ABT-518[7]	All	Global	-	-	-	4	16	29	71	107	164	184	205	206	207	1,193
ABT-594[4][5]	Chron. Perc. Pain	Global	-	13	36	70	111	159	200	206	197	189	184	180	169	1,714
ABT-594[6]	Neuro Pain	Global	-	21	99	72	125	169	209	220	224	219	213	205	195	1,971
ABT-594[7]	Nociceptive Pain	Global	-	-	3	9	15	22	29	34	35	35	35	34	34	285
ABT-773[9]	Tablet	Global	9	102	172	241	306	362	364	358	343	327	312	297	283	3,476
ABT-773[9]	IV	Global	-	-	18	38	53	68	80	86	86	85	83	81	65	743
ABT-773[9]	Japan	Global	-	-	9	23	36	53	61	61	61	58	55	53	50	520
Subtotal			*9*	*136*	*337*	*457*	*662*	*862*	*1,014*	*1,072*	*1,110*	*1,097*	*1,087*	*1,056*	*1,003*	*9,902*
Other Program Compounds (As of Most Recent Documentation: December 2005)[2]																
ABT-510	Non-Sarcoma	US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-510	Non-Sarcoma	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-751	All	US[3]	-	-	-	-	-	-	2	4	9	23	42	52	30	162
ABT-751	All	Ex-US[10]	-	-	-	-	-	-	1	7	12	40	90	115	65	330
ABT-627	Non PCA	US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Non PCA	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	HRPCA	US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	HRPCA	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Japan	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Ph IV Studies	US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-627	Ph IV Studies	Ex-US	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-100	All	Global	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-724	All	Global	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-492	All	Global	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Subtotal (Actual Scenario)			-	-	-	-	-	-	*3*	*11*	*21*	*63*	*132*	*166*	*95*	*492*
Nominal Net Sales (But-for Scenario)			9	136	337	457	662	862	1,017	1,083	1,131	1,160	1,219	1,222	1,098	10,394

Note:
(1) Nominal Net Sales forecasts for Non-viable Program Compounds taken from Abbott "Total Low" sales projections.
(2) Nominal Net Sales forecasts from "2006 LRP" sales projections (ABBT 299286-299297 and ABBT 299147-299158). Only the "Expected Commercial" sales forecast was provided, described by Abbott as a combination of the Low, Base and Upside scenarios. Therefore, Nominal Sales utilized in the Low Case have been estimated based on the historical relationship between the Low, Base and Upside forecasts and the "Expected Commercial" forecast on a compound by compound basis.
(3) See ABBT 0003362 - 0003364.
(4) See ABBT 0003365 - 0003367.
(5) "Total Low" sales not available. "Total Base" sales used.
(6) See ABBT 0003368 - 0003370.
(7) See ABBT 0003416 - 003418.
(8) See ABBT 329442 - 329558 .
(9) See ABBT 299286 - 299297.
(10) See ABBT 299147 - 299158.
(11) Nominal Net Sales have decreased from $7.2 billion (initial report) to $492m (12/3/2007 updated report) in the Actual Scenario, and in effect have decreased from $17.1 billion (initial report) to $10.4 billion (12/3/2007 updated report) in the But-for Scenario, based loss of proje sales for ABT-510 and ABT-627 due to their recent terminations. Although ABT-751 is still under development, its forecasted nominal sales reflects its status as of December 2005.
Differences are due to rounding

Exhibit 4.6
LOW CASE
Expected Hancock Milestones by Compound - "But-for" Scenario[1][3]
($millions)

Program Compound	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals[3]
Misrepresented Program Compounds (As of Agreement Date: March 13, 2001)														
ABT-518	-	-	-	1	-	-	-	-	-	-	-	-	-	1
ABT-594	-	2	-	-	-	-	-	-	-	-	-	-	-	2
ABT-773	-	15	-	-	-	-	-	-	-	-	-	-	-	15
Subtotal	-	*17*	-	*1*	-	-	-	-	-	-	-	-	-	*17*
Other Program Compounds (As of Most Recent Documentation: December 2005)														
ABT-510	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-751	-	-	-	-	-	-	1	-	-	-	-	-	-	1
ABT-627	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-100	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-724	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-492	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Subtotal	-	-	-	-	-	-	*1*	-	-	-	-	-	-	*1*
Expected Hancock Milestones	-	17	-	1	-	-	1	-	-	-	-	-	-	18

Notes:
(1) Nominal milestone forecast X projected success rates (see Exhibit 4.8 and 5.1). Success rate for Compound Indication with the highest probability of launch applied to the corresponding Nominal Projected Milestone Payment for each Compound.
(2) Aggregate Milestone Payment Cap: $40M (see JH 008078 - 008211, Article 6).
(3) Expected Milestone Payments to Hancock have decreased from $22m (initial report) to $18m (12/3/2007 updated report) based on the decreased Nominal Milestone Payments (see Exhibit 4.8).
Differences are due to rounding

Exhibit 4.7
LOW CASE
Expected Hancock Milestones by Compound - "Actual" Scenario[1][5]
($millions)

Program Compound	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals[3]
Misrepresented Program Compounds (As of Agreement Date: March 13, 2001) [3]														
ABT-518	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-594	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-773	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Subtotal	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other Program Compounds (As of Most Recent Documentation: December 2005)														
ABT-510	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-751[4]	-	-	-	-	-	-	2	-	-	-	-	-	-	2
ABT-627	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-100	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-724	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-492	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Subtotal	-	-	-	-	-	-	2	-	-	-	-	-	-	2
Expected Hancock Milestones	-	-	-	-	-	-	2	-	-	-	-	-	-	2

Note:
(1) Nominal milestone forecast X projected success rates (see Exhibit 4.8 and 5.1). Success rate for Compound Indication with the highest probability of launch applied to the corresponding Nominal Projected Milestone Payment for each Compound.
(2) Aggregate Milestone Payment Cap: $40M (see JH 008078 - 008211, Article 6).
(3) Misrepresented Program Compounds have an assumed 0% success rate.
(4) Nominal Milestone payment forecast for ABT-751 is $20 million. ABT-751 expected to be the first Program Compound to receive FDA Approval.
(5) Expected Milestone Payments to Hancock have decreased from $9m (initial report) to $2m (12/3/2007 updated report) based on the decreased Nominal Milestone Payments (see Exhibit 4.8).
Differences are due to rounding

Exhibit 4.8

Nominal FDA Approval Milestone Payment Forecast by Program Compound

($millions)

Program Compound	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Totals
Misrepresented Program Compounds (As of Agreement Date: March 13, 2001)														
ABT-518	-	-	-	10	-	-	-	-	-	-	-	-	-	10
ABT-594	-	10	-	-	-	-	-	-	-	-	-	-	-	10
ABT-773	-	20[1]	-	-	-	-	-	-	-	-	-	-	-	20
Subtotal	-	*30*	-	*10*	-	-	-	-	-	-	-	-	-	40
Other Program Compounds (As of Most Recent Documentation: December 2005) [3]														
ABT-510	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-751	-	-	-	-	-	-	20[2]	-	-	-	-	-	-	20
ABT-627	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-100	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-724	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ABT-492	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Subtotal	-	-	-	-	-	-	*20*	-	-	-	-	-	-	*20*
Nominal Net Milestones	-	30	-	10	-	-	20	-	-	-	-	-	-	60

Note:
(1) Assuming all Program Compounds were viable ("But-for" scenario), ABT-773 was expected to be the first Program Compound to receive FDA Approval (see JH 008133 - JH 008132). $20 million milestone payment applies to first approval. $10 milestone payment applies to subsequent approvals.
(2) Assuming Progam Compunds ABT-518, ABT-594, and ABT-773 were Non-viable ("Actual" scenario), ABT-751 is expected to be the first Program Compound to receive FDA Approval. $20 million milestone payment applies to first approval. $10 million milestone payment applies to subsequent approvals.
(3) Status of the Other Program Compounds has been updated to reflect its current status; therefore, forecasted nominal milestone payments for ABT-510 and ABT-627 have been reduced to 0 due to recent terminations. Although ABT-751 is still under development, its projected launch date reflects its status and as of December 2005.
Differences are due to rounding

Exhibit 5.1

Comparison of Industry and Company Projected Success Rates by Compound Indication

Program Compound	Indication	Region	Therapy	Stage of Development	BASE CASE Abbott Projected[1]	LOW CASE CMR International (2004)[2]	Pharma Predict (2006)[3]	DiMasi (1995)[4]	DiMasi (2001)[5]	Abbott Historical[6]
Misrepresented Program Compounds (As of Agreement Date: March 13, 2001)										
ABT-518	All	Global	Anticancer	Phase I	12.5%	6.0%	23%	23%	22%	21%
ABT-594	Chron. Pero. Pain	Global	Analgesic, Other	Phase II	16.0%	17.0%	26%	31%	30%	38%
ABT-594	Neuro Pain	Global	Analgesic, Other	Phase II	31.5%	17.0%	26%	31%	30%	38%
ABT-594	Nociceptive Pain	Global	Analgesic, Other	Phase II	7.5%	17.0%	26%	31%	30%	38%
ABT-773	Tablet	Global	Anti-Infective	Phase III	72.0%	75.2%	84%	77%	69%	67%
ABT-773	IV	Global	Anti-Infective	Phase I	36.0%	33.2%	50%	30%	22%	21%
ABT-773	Japan	Global	Anti-Infective	Phase I	37.4%	33.2%	50%	30%	22%	21%
Other Program Compounds (As of Most Recent Documentation: December 2005) [7]										
ABT-510	Non-Sarcoma	US	Anticancer	Terminated	0.0%	0.0%	0%	0%	0%	0%
ABT-510	Non-Sarcoma	Ex-US	Anticancer	Terminated	0.0%	0.0%	0%	0%	0%	0%
ABT-751	All	US	Anticancer	Phase II	41.0%	8.0%	35%	31%	30%	38%
ABT-751	All	Ex-US	Anticancer	Phase II	41.0%	8.0%	35%	31%	30%	38%
ABT-627	Non PCA	US	Anticancer	Terminated	0.0%	0.0%	0%	0%	0%	0%
ABT-627	Non PCA	Ex-US	Anticancer	Terminated	0.0%	0.0%	0%	0%	0%	0%
ABT-627	HRPCA	US	Anticancer	Terminated	0.0%	0.0%	0%	0%	0%	0%
ABT-627	HRPCA	Ex-US	Anticancer	Terminated	0.0%	0.0%	0%	0%	0%	0%
ABT-627	Japan	Ex-US	Anticancer	Terminated	0.0%	0.0%	0%	0%	0%	0%
ABT-627	Ph IV Studies	US	Anticancer	Terminated	0.0%	0.0%	0%	0%	0%	0%
ABT-627	Ph IV Studies	Ex-US	Anticancer	Terminated	0.0%	0.0%	0%	0%	0%	0%
ABT-100	All	Global	Anticancer	Terminated	0.0%	0.0%	0%	0%	0%	0%
ABT-724	All	Global	MED	Terminated	0.0%	0.0%	0%	0%	0%	0%
ABT-492	All	Global	Anti-Infective	Terminated	0.0%	0.0%	0%	0%	0%	0%

Notes:

(1) Abbott Compound Specific success rates utilized for Base Case damage computations (see Exhibit 5.2).
(2) 2004 CMR International success rates utilized for Low Case damage computations (see Exhibit 5.3).
(3) www.pharmapredict.com.
(4) JH001340 - 001361
(5) DiMasi, et al., 2001, "The price of innovation: new estimates of drug development costs." www.cptech.org/ip/health/econ/dimasi2003.pdf.
(6) ABBT 304846 - 304862.
(7) Status of the Other Program Compounds has been updated to reflect terminations that have occurred through December 1, 2007; therefore, the probabilities of success for ABT-510 and ABT-627 have been reduced to 0%. Although ABT-751 is still alive, its probability of success reflects its status as of December 2005.
Differences are due to rounding

Exhibit 5.2
BASE CASE
Abbott Projected Success Rates by Compound Indication

Program Compound	Indication	Region	Stage of Development	Completion of Preclinical Phase	Completion of Phase I	Completion of Phase II	Completion of Phase III	FDA Approval	Probability of Launch from Stage of Development[1]
Misrepresented Program Compounds (As of Agreement Date: March 13, 2001) [2]									
ABT-518	All	Global	Phase I	-	50%	50%	50%	n/a	12.5%
ABT-594	Chron. Perc. Pain	Global	Phase II	-	-	50%	32%	n/a	16.0%
ABT-594	Neuro Pain	Global	Phase II	-	-	45%	70%	n/a	31.5%
ABT-594	Nociceptive Pain	Global	Phase II	-	-	50%	15%	n/a	7.5%
ABT-773	Tablet	Global	Phase III	-	-	-	80%	90%	72.0%
ABT-773	IV	Global	Phase I	-	100%	50%	80%	90%	36.0%
ABT-773	Japan	Global	Phase I	-	65%	100%	64%	90%	37.4%
Other Program Compounds (As of Most Recent Documentation: December 2005) [3][4]									
ABT-510	Non-Sarcoma	US	Terminated	-	-	-	-	-	0.0%
ABT-510	Non-Sarcoma	Ex-US	Terminated	-	-	-	-	-	0.0%
ABT-751	All	US	Phase II	-	-	65%	70%	90%	41.0%
ABT-751	All	Ex-US	Phase II	-	-	65%	70%	90%	41.0%
ABT-627	Non PCA	US	Terminated	-	-	-	-	-	0.0%
ABT-627	Non PCA	Ex-US	Terminated	-	-	-	-	-	0.0%
ABT-627	HRPCA	US	Terminated	-	-	-	-	-	0.0%
ABT-627	HRPCA	Ex-US	Terminated	-	-	-	-	-	0.0%
ABT-627	Japan	Ex-US	Terminated	-	-	-	-	-	0.0%
ABT-627	Ph IV Studies	US	Terminated	-	-	-	-	-	0.0%
ABT-627	Ph IV Studies	Ex-US	Terminated	-	-	-	-	-	0.0%
ABT-100	All	Global	Terminated	-	-	-	-	-	0.0%
ABT-724	All	Global	Terminated	-	-	-	-	-	0.0%
ABT-492	All	Global	Terminated	-	-	-	-	-	0.0%

Note:
(1) PC x Phase I x Phase II x Phase III x FDA Approval.
(2) ABT-518 All (ABBT 292465); ABT-594 Chronic. Perc. Pain (ABBT 292382 & 287552); ABT - 594 Neuro Pain (ABBT 292381); ABT-594 Nociceptive Pain (ABBT 0003416); ABT-773 Tablet (ABBT 292393); ABT-773 IV (ABBT 292394); ABT-773 Japan (ABBT 292395).
(3) ABBT 250741 - 250751
(4) Status of the Other Program Compounds has been updated to reflect terminations that have occurred through December 1, 2007; therefore, the probabilities of success for ABT-510 and ABT-627 have been reduced to 0%. Although ABT-751 is still being developed, its probability of success reflects its status as of December 2005.
Differences are due to rounding

Exhibit 5.3
LOW CASE
2004 CMR International Success Rates by Compound Indication[1]

Program Compound	Indication	Region	Stage of Development	Completion of Preclinical Phase	Completion of Phase I	Completion of Phase II	Completion of Phase III	FDA Approval	Probability of Launch from Stage of Development[2]
Misrepresented Program Compounds (As of Agreement Date: March 13, 2001)									
ABT-518	All	Global	Phase I	-	75%	25%	40%	80%	6.0%
ABT-594	Chron. Perc. Pain	Global	Phase II	-	-	31%	63%	87%	17.0%
ABT-594	Neuro Pain	Global	Phase II	-	-	31%	63%	87%	17.0%
ABT-594	Nociceptive Pain	Global	Phase II	-	-	31%	63%	87%	17.0%
ABT-773	Tablet	Global	Phase III	-	-	-	94%	80%	75.2%
ABT-773	IV	Global	Phase I	-	70%	63%	94%	80%	33.2%
ABT-773	Japan	Global	Phase I	-	70%	63%	94%	80%	33.2%
Other Program Compounds (As of Most Recent Documentation: December 2005) [3]									
ABT-510	Non-Sarcoma	US	Terminated	-	-	-	-	-	0.0%
ABT-510	Non-Sarcoma	Ex-US	Terminated	-	-	-	-	-	0.0%
ABT-751	All	US	Phase II	-	-	25%	40%	80%	8.0%
ABT-751	All	Ex-US	Phase II	-	-	25%	40%	80%	8.0%
ABT-627	Non PCA	US	Terminated	-	-	-	-	-	0.0%
ABT-627	Non PCA	Ex-US	Terminated	-	-	-	-	-	0.0%
ABT-627	HRPCA	US	Terminated	-	-	-	-	-	0.0%
ABT-627	HRPCA	Ex-US	Terminated	-	-	-	-	-	0.0%
ABT-627	Japan	Ex-US	Terminated	-	-	-	-	-	0.0%
ABT-627	Ph IV Studies	US	Terminated	-	-	-	-	-	0.0%
ABT-627	Ph IV Studies	Ex-US	Terminated	-	-	-	-	-	0.0%
ABT-100	All	Global	Terminated	-	-	-	-	-	0.0%
ABT-724	All	Global	Terminated	-	-	-	-	-	0.0%
ABT-492	All	Global	Terminated	-	-	-	-	-	0.0%

Note:
(1) ABBT 308584 - 308645
(2) PC x Phase I x Phase II x Phase III x FDA Approval.
(3) Status of the Other Program Compounds has been updated to reflect terminations that have occurred through December 1, 2007; therefore, the probabilities of success for ABT-510 and ABT-627 have been reduced to 0%. Although ABT-751 is still being developed, its probability of success reflects its status as of December 2005.
Differences are due to rounding

Exhibit 6.1

Aggregate Spending Shortfall Computation[1]

($millions)

	Totals[2]	Totals[3]
Aggregate Spending Target[1]	614.0	614.0
LESS Abbott's Actual Aggregate Spending During Program Term (2001 - 2004)[2]	456.2	442.0
Aggregate Carryover Amount	157.8	172.0
LESS Abbott's Actual 2005 Spending	73.0	72.9
Unspent Aggregate Carryover Amount	84.8	99.1
1/3 of Unspent Aggregate Carryover Amount[1]	28.3	33.0
Pre-judgment Interest[4]	2.77	3.24

Note:
(1) JH 008078 - 008211, Research Funding Agreement, Section 3.3(b).
(2) See Exhibit 6.2.
(3) See Exhibit 6.3.
(4) Assumes payment due January 30, 2006 (See Paragraph 22 of the report). Under Illinois law the statutory rate of 5% is available on damages resulting from a breach of contract. See 815 ILCS Sec. 205/2 ; Transportation & Train Assoc. v. Morrison Knudsen Corp., 225 F.3d 397 (7th Cir. 2001). The same is true for cases arising in equity. See In re Estate v. Wernick, 535 N.E. 2d 876 (Ill. S.Ct. 1989). We have assumed the 5% statutory rate as a reasonable rate of pre-judgment interest
Differences are due to rounding

Exhibit 6.2

Reported Program Spending by Compound

Based upon Abbott Laboratories Amended Responses, 2nd Set of Interrogatories

($millions)

	Reported Actual[1]				
Program Compound	2001[2]	2002	2003	2004	2005
ABT-773	59.7	13.9	(0.9)	0.3	-
ABT-627	28.7	51.8	53.6	43.4	44.6
ABT-594	5.5	1.4	-	-	-
ABT-751	5.3	9.7	11.0	13.5	12.3
ABT-492	20.1	32.8	4.1	-	-
ABT-510	7.2	12.8	18.5	23.6	16.1
ABT-518	2.4	-	-	-	-
ABT-100	7.5	2.4	-	-	-
ABT-724	6.6	6.5	0.8	-	-
All Program Compounds	143.0	131.3	87.1	80.8	73.0
Management Fees / Milestones to Hancock	-	10.0	2.0	2.0	-
Total Spending	143.0	141.3	89.1	82.8	73.0
Cumulative Spending	143.0	284.3	373.4	456.2	529.2

Note:
(1) Amounts reported in the 2006 Annual Research Plan (ABBT 372289 - 372299). No detailed information has become available pertaining to the compilation of these development costs. If this information is made available by Abbott, along with deposition testimony and other discovery documents, I may amend this schedule.
(2) Reported Actual Spending is changed based on Abbott Laboratories Amended Responses and Objections to Plaintiff's Second Set of Interrogatories (August 3, 2007).
(3) 2001 Actual Spending has been decreased to account for spending during the Program Term only, March 13 - December 31. March spending is pro-rated evenly per diem.

Exhibit 6.3

Reported Program Spending by Compound

Based upon Research Funding Plan Update (November 20, 2007)

($millions)

	Reported Actual[1]				
Program Compound	2001[1]	2002	2003	2004	2005
ABT-773	65.4	15.7	(0.9)	0.3	-
ABT-627	27.3	49.4	53.6	43.2	44.4
ABT-594	6.2	1.4	-	-	-
ABT-751	5.2	9.6	11.0	13.5	12.3
ABT-492	16.1	28.2	4.1	-	-
ABT-510	7.0	12.3	18.5	23.6	16.2
ABT-518	3.0	-	-	-	-
ABT-100	2.9	2.4	-	-	-
ABT-724	2.6	5.5	0.8	-	-
All Program Compounds	135.8	124.5	87.1	80.6	72.9
Management Fees / Milestones to Hancock	-	10.0	2.0	2.0	-
Total Spending	135.8	134.5	89.1	82.6	72.9
Cummulative Spending	135.8	270.3	359.4	442.0	514.9

Note:
(1) 2008 Research Funding Plan Update (November 20, 2007).
(2) 2001 Spending is adjusted, on a daily pro-rata basis, to account for only the Program Term, March 13 - December 31.

Exhibit 7.1
Agreement Rescission Computation
($millions)

John Hancock Payments to Abbott[1]	
2001 John Hancock Program Payment	50
2002 John Hancock Program Payment	54
	104
Less: Abbott Payments to John Hancock	
Management Fees[2]	6
Milestone Payment[1],[2]	8
Wakunuga Licensing (ABT-492)	0.4
	14
Total Rescission Payment	89.6
Pre-judgement Interest[3]	28.4

Note:
(1) See AL 002056 - 002059.
(2) See ABBT 372289 - 372299.

(3) Under Illinois law the statutory rate of 5% is available on damages resulting from a breach of contract. See 815 ILCS Sec. 205/2 ; Transportation & Train Assoc. v. Morrison Knudsen Corp., 225 F.3d 397 (7th Cir. 2001). The same is true for cases arising in equity . See In re Estate v. Wernick, 535 N.E. 2d 876 (Ill. S.Ct. 1989). We have assumed the 5% statutory rate as a reasonable rate of pre-judgment interest

Exhibit 8.1

Plaintiff John Hancock's Response to Interrogatory #21

Lost Royalty and Lost Milestone Payment Summary for ABT-518 Only ($millions)

Lost Royalty Payment Summary	Base Case ($ millions)	Low Case ($ millions)
But-for Scenario Royalty Payments	65	9
Actual Scenario Royalty Payments	34	3
Lost Royalty Payments - Nominal	31	6
Lost Royalty Payments[1]	26	5

Lost Milestone Payment Summary	Base Case ($ millions)	Low Case ($ millions)
But-for Scenario Milestone Payments	7	2
Actual Scenario Milestone Payments	8	2
Lost Milestone Payments - Nominal	(2)	0
Lost Milestone Payments[1]	(1)	0
Total Lost Royalty and Milestone Payments[1]	24	5

(1) Amount computed reflects the nominal value of past damages plus the present value of future damages, as of December 31, 2007. Pre-judgment interest has been computed as $.1 million (Base Case) and $.1 million (Low Case). Under Illinois law the statutory rate of 5% is available on damages resulting from a breach of contract. See 815 ILCS Sec. 205/2 ; Transportation & Train Assoc. v. Morrison Knudsen Corp., 225 F.3d 397 (7th Cir. 2001). The same is true for cases arising in equity . See In re Estate v. Wernick, 535 N.E. 2d 876 (Ill. S.Ct. 1989). We have assumed the 5% statutory rate as a reasonable rate of pre-judgment interest.
Differences are due to rounding

Explanatory Note A: This computation of lost royalty and milestone payments for ABT-518 only, has been computed solely to update the response to Interrogatory Question #21 for the recent termination of ABT-510 and ABT-627, and does not represent an amendment to the Expert Report of Alan Friedman dated October 13, 2006. This model, for the purposes of addressing Interrogatory Question #21, assumes a hypothetical case in which lost royalty and milestone payments are computed on one single compound.

Exhibit 8.2

Plaintiff John Hancock's Response to Interrogatory #22

Lost Royalty and Lost Milestone Payment Summary for ABT-594 Only

($millions)

Lost Royalty Payment Summary	Base Case ($ millions)	Low Case ($ millions)
But-for Scenario Royalty Payments	181	49
Actual Scenario Royalty Payments	34	3
Lost Royalty Payments - Nominal	147	46
Lost Royalty Payments[1]	131	41

Lost Milestone Payment Summary	Base Case ($ millions)	Low Case ($ millions)
But-for Scenario Milestone Payments	7	4
Actual Scenario Milestone Payments	8	2
Lost Milestone Payments - Nominal	(1)	3
Lost Milestone Payments[1]	(1)	3
Total Lost Royalty and Milestone Payments[1]	131	43

(1) Amount computed reflects the nominal value of past damages plus the present value of future damages, as of December 31, 2007. Pre-judgment interest has been computed as $1.5 million (Base Case) and $0.9 million (Low Case). Under Illinois law the statutory rate of 5% is available on damages resulting from a breach of contract. See 815 ILCS Sec. 205/2 ; Transportation & Train Assoc. v. Morrison Knudsen Corp., 225 F.3d 397 (7th Cir. 2001). The same is true for cases arising in equity . See In re Estate v. Wernick, 535 N.E. 2d 876 (Ill. S.Ct. 1989). We have assumed the 5% statutory rate as a reasonable rate of pre-judgment interest.
Differences are due to rounding

Explanatory Note A: This computation of lost royalty and milestone payments for ABT-594 only, has been computed solely to update the response to Interrogatory Question #22 for the recent termination of ABT-510 and ABT-627, and does not represent an amendment to the Expert Report of Alan Friedman dated October 13, 2006. This model, for the purposes of addressing Interrogatory Question #22, assumes a hypothetical case in which lost royalty and milestone payments are computed on one single compound.

Exhibit 8.3

Plaintiff John Hancock's Response to Interrogatory #23

Lost Royalty and Lost Milestone Payment Summary for ABT-773 Only

($millions)

Lost Royalty Payment Summary	Base Case ($ millions)	Low Case ($ millions)
But-for Scenario Royalty Payments	328	201
Actual Scenario Royalty Payments	34	3
Lost Royalty Payments - Nominal	294	198
Lost Royalty Payments[1]	271	181

Lost Milestone Payment Summary	Base Case ($ millions)	Low Case ($ millions)
But-for Scenario Milestone Payments	18	16
Actual Scenario Milestone Payments	8	2
Lost Milestone Payments - Nominal	10	14
Lost Milestone Payments[1]	11	14
Total Lost Royalty and Milestone Payments[1]	281	196

(1) Amount computed reflects the nominal value of past damages plus the present value of future damages, as of December 31, 2007. Pre-judgment interest has been computed as $7.6 million (Base Case) and $5.6 million (Low Case). Under Illinois law the statutory rate of 5% is available on damages resulting from a breach of contract. See 815 ILCS Sec. 205/2 ; Transportation & Train Assoc. v. Morrison Knudsen Corp., 225 F.3d 397 (7th Cir. 2001). The same is true for cases arising in equity . See In re Estate v. Wemick, 535 N.E. 2d 876 (Ill. S.Ct. 1989). We have assumed the 5% statutory rate as a reasonable rate of pre-judgment interest.
Differences are due to rounding

Explanatory Note A: This computation of lost royalty and milestone payments for ABT-773 only, has been computed solely to update the response to Interrogatory Question #23 for the recent termination of ABT-510 and ABT-627, and does not represent an amendment to the Expert Report of Alan Friedman dated October 13, 2006. This model, for the purposes of addressing Interrogatory Question #23, assumes a hypothetical case in which lost royalty and milestone payments are computed on one single compound.

Exhibit 9.1
BASE CASE
2003 'But-for' Annual Research Plan Scenarios

Scenario as of Planning Period (Q4 2002)[1][2]				2001-2002 Actual Spending ($ millions)[3]		2003-2004 Expected Spending ($millions)[4]				2003 Final Plan (Other Spending)		TOTAL	Hancock 2003 Payment?	Expected Payment	
'But-for' Scenario	[A] ABT-518	[B] ABT-594	[C] ABT-773	ABT-518	ABT-594	ABT-773	ABT-518	ABT-594	ABT-773	All Other Compounds 4-year spending[5]	Milestone and Management Fees 4-year spending[6]	4-year Forecast Scenario	*if >$614m then yes*	*Scenario Probability[7]*	*Expected Payment Value*
1	25% Active (Phase 2)	32% Active (Phase 3)	72% Active (Filed)	37	73	143	36	36	72	354	23	774	Yes	6%	3.3
2	25% Active (Phase 2)	32% Active (Phase 3)	8% Failed (Filing)	37	73	162	36	36	0	354	23	720	Yes	1%	0.4
3	25% Active (Phase 2)	14% Failed (Phase 3)	72% Active (Filed)	37	66	143	36	0	72	354	23	731	Yes	2%	1.4
4	25% Active (Phase 2)	14% Failed (Phase 3)	8% Failed (Filing)	37	66	162	36	0	0	354	23	677	Yes	0%	0.2
5	25% Failed (Phase 2)	32% Active (Phase 3)	72% Active (Filed)	46	73	143	0	36	72	354	23	748	Yes	6%	3.3
6	25% Failed (Phase 2)	32% Active (Phase 3)	8% Failed (Filing)	46	73	162	0	36	0	354	23	694	Yes	1%	0.4
7	25% Failed (Phase 2)	14% Failed (Phase 3)	72% Active (Filed)	46	66	143	0	0	72	354	23	705	Yes	2%	1.4
8	25% Failed (Phase 2)	14% Failed (Phase 3)	8% Failed (Filing)	46	66	162	0	0	0	354	23	652	Yes	0%	0.2
9	25% Active (Phase 2)	32% Active (Phase 3)	20% Failed (Phase 3)	37	73	73	36	36	0	354	23	631	Yes	2%	0.9
10	25% Active (Phase 2)	14% Failed (Phase 3)	20% Failed (Phase 3)	37	66	73	36	0	0	354	23	589	No	1%	0.0
11	25% Active (Phase 2)	55% Failed (Phase 2)	72% Active (Filed)	37	12	143	36	0	72	354	23	676	Yes	10%	5.7
12	25% Active (Phase 2)	55% Failed (Phase 2)	8% Failed (Filing)	37	12	162	36	0	0	354	23	623	Yes	1%	0.6
13	25% Active (Phase 2)	55% Failed (Phase 2)	20% Failed (Phase 3)	37	12	73	36	0	0	354	23	534	No	3%	0.0
14	25% Failed (Phase 2)	32% Active (Phase 3)	20% Failed (Phase 3)	46	73	73	0	36	0	354	23	606	No	2%	0.0
15	25% Failed (Phase 2)	14% Failed (Phase 3)	20% Failed (Phase 3)	46	66	73	0	0	0	354	23	563	No	1%	0.0

Exhibit 9.1
BASE CASE
2003 'But-for' Annual Research Plan Scenarios

	Scenario as of Planning Period (Q4 2002)[1][2]			2001-2002 Actual Spending ($ millions)[3]		2003-2004 Expected Spending ($millions)[4]				2003 Final Plan (Other Spending)		TOTAL	Hancock 2003 Payment?	Expected Payment	
'But-for' Scenario	[A] ABT-518	[B] ABT-594	[C] ABT-773	ABT-518	ABT-594	ABT-773	ABT-518	ABT-594	ABT-773	All Other Compounds 4-year spending[5]	Milestone and Management Fees 4-year spending[6]	4-year Forecast Scenario	*if >$614m then yes*	*Scenario Probability[7]*	*Expected Payment Value*
16	25% Failed (Phase 2)	55% Failed (Phase 2)	72% Active (Filed)	46	12	143	0	0	72	354	23	650	Yes	10%	5.7
17	25% Failed (Phase 2)	55% Failed (Phase 2)	8% Failed (Filing)	46	12	162	0	0	0	354	23	597	No	1%	0.0
18	25% Failed (Phase 2)	55% Failed (Phase 2)	20% Failed (Phase 3)	46	12	73	0	0	0	354	23	508	No	3%	0.0
19	50% Failed (Phase 1)	32% Active (Phase 3)	72% Active (Filed)	4	73	143	0	36	72	354	23	705	Yes	11%	6.6
20	50% Failed (Phase 1)	32% Active (Phase 3)	8% Failed (Filing)	4	73	162	0	36	0	354	23	652	Yes	1%	0.7
21	50% Failed (Phase 1)	32% Active (Phase 3)	20% Failed (Phase 3)	4	73	73	0	36	0	354	23	563	No	3%	0.0
22	50% Failed (Phase 1)	14% Failed (Phase 3)	72% Active (Filed)	4	66	143	0	0	72	354	23	663	Yes	5%	2.8
23	50% Failed (Phase 1)	14% Failed (Phase 3)	8% Failed (Filing)	4	66	162	0	0	0	354	23	609	No	1%	0.0
24	50% Failed (Phase 1)	14% Failed (Phase 3)	20% Failed (Phase 3)	4	66	73	0	0	0	354	23	520	No	1%	0.0
25	50% Failed (Phase 1)	55% Failed (Phase 2)	72% Active (Filed)	4	12	143	0	0	72	354	23	608	No	20%	0.0
26	50% Failed (Phase 1)	55% Failed (Phase 2)	8% Failed (Filing)	4	12	162	0	0	0	354	23	555	No	2%	0.0
27	50% Failed (Phase 1)	55% Failed (Phase 2)	20% Failed (Phase 3)	4	12	73	0	0	0	354	23	466	No	6%	0.0
														100%	33.6

Notes:
(1) Program Compounds either succeeded through 2002 and are still currently in development as of 4Q 2002 ("Active") or were terminated in 2001 or 2002 and are no longer in development as of this date ("Failed").
(2) Probabilities represent the probability of each drug reaching a specific stage of development.
(3) Actual Spending equals planned nominal spending in 2001-2002 assuming the compound has not been terminated.
(4) Expected Spending equals forecasted nominal spending multiplied by the cumulative probability of launch for each compound.
(5) Actual spending as of 2003 Plan + Forecast Spending through 2004 for 6 other compounds.
(6) Actual spending as of 2003 Plan + Forecast Spending through 2004 for certain milestone and management fees paid to Hancock.
(7) Scenario Probability = [A] x [B] x [C]

Exhibit 9.2
BASE CASE
2004 'But-for' Annual Research Plan Scenarios

	Scenario as of Planning Period (Q4 2003)[1][2]			2001-2003 Actual Spending ($ millions)[2]			2004 Expected Spending ($ millions)[2]			2003 Final Plan (Other Spending)		TOTAL	Hancock 2003 Payment?	Expected Payment	
'But-for' Scenario	[A] ABT-518	[B] ABT-594	[C] ABT-773	ABT-518	ABT-594[3]	ABT-773	ABT-518	ABT-594[3]	ABT-773	All Other Compounds 4-year spending[4]	Milestone and Management Fees 4-year spending[5]	4-year Forecast Scenario	*if >$614m then yes*	*Scenario Probability[6]*	*Expected Payment Value*
1	13% Active (Phase 3)	32% Active (Phase 3)	72% Active (Filing)	72	105	188	22	15	32	362	23	819	Yes	3%	1.5
2	13% Failed (Phase 3)	32% Active (Phase 3)	72% Active (Filing)	86	105	188	0	15	32	362	23	811	Yes	3%	1.5
3	13% Active (Phase 3)	32% Active (Phase 3)	8% Failed (Filing)	72	105	162	22	15	0	362	23	761	Yes	0%	0.2
4	13% Failed (Phase 3)	32% Active (Phase 3)	8% Failed (Filing)	86	105	162	0	15	0	362	23	754	Yes	0%	0.2
5	13% Active (Phase 3)	14% Failed (Phase 3)	72% Active (Filing)	72	66	188	22	0	32	362	23	765	Yes	1%	0.6
6	13% Failed (Phase 3)	14% Failed (Phase 3)	72% Active (Filing)	86	66	188	0	0	32	362	23	758	Yes	1%	0.6
7	13% Active (Phase 3)	14% Failed (Phase 3)	8% Failed (Filing)	72	66	162	22	0	0	362	23	707	Yes	0%	0.1
8	13% Failed (Phase 3)	14% Failed (Phase 3)	8% Failed (Filing)	86	66	162	0	0	0	362	23	700	Yes	0%	0.1
9	25% Failed (Phase 2)	32% Active (Phase 3)	72% Active (Filing)	46	105	188	0	15	32	362	23	772	Yes	6%	2.9
10	25% Failed (Phase 2)	32% Active (Phase 3)	8% Failed (Filing)	46	105	162	0	15	0	362	23	714	Yes	1%	0.3
11	25% Failed (Phase 2)	14% Failed (Phase 3)	72% Active (Filing)	46	66	188	0	0	32	362	23	718	Yes	2%	1.3
12	25% Failed (Phase 2)	14% Failed (Phase 3)	8% Failed (Filing)	46	66	162	0	0	0	362	23	660	Yes	0%	0.1
13	13% Active (Phase 3)	32% Active (Phase 3)	20% Failed (Phase 3)	72	105	73	22	15	0	362	23	672	Yes	1%	0.4
14	13% Failed (Phase 3)	32% Active (Phase 3)	20% Failed (Phase 3)	86	105	73	0	15	0	362	23	665	Yes	1%	0.4
15	13% Active (Phase 3)	14% Failed (Phase 3)	20% Failed (Phase 3)	72	66	73	22	0	0	362	23	618	Yes	0%	0.2
16	13% Failed (Phase 3)	14% Failed (Phase 3)	20% Failed (Phase 3)	86	66	73	0	0	0	362	23	611	No	0%	0.0
17	13% Active (Phase 3)	55% Failed (Phase 2)	72% Active (Filing)	72	12	188	22	0	32	362	23	710	Yes	5%	2.6
18	13% Failed (Phase 3)	55% Failed (Phase 2)	72% Active (Filing)	86	12	188	0	0	32	362	23	703	Yes	5%	2.6

Exhibit 9.2
BASE CASE
2004 'But-for' Annual Research Plan Scenarios

	Scenario as of Planning Period (Q4 2003)[1][2]			2001-2003 Actual Spending ($ millions)[3]			2004 Expected Spending ($ millions)[4]			2003 Final Plan (Other Spending)		TOTAL	Hancock 2003 Payment?	Expected Payment	
'But-for' Scenario	[A] ABT-518	[B] ABT-594	[C] ABT-773	ABT-518	ABT-594[5]	ABT-773	ABT-518	ABT-594[5]	ABT-773	All Other Compounds 4-year spending[6]	Milestone and Management Fees 4-year spending[7]	4-year Forecast Scenario	*if >$614m then yes*	*Scenario Probability*[8]	*Expected Payment Value*
19	13% Active (Phase 3)	55% Failed (Phase 2)	8% Failed (Filing)	72	12	162	22	0	0	362	23	652	Yes	1%	0.3
20	13% Failed (Phase 3)	55% Failed (Phase 2)	8% Failed (Filing)	86	12	162	0	0	0	362	23	645	Yes	1%	0.3
21	13% Active (Phase 3)	55% Failed (Phase 2)	20% Failed (Phase 3)	72	12	73	22	0	0	362	23	563	No	1%	0.0
22	13% Failed (Phase 3)	55% Failed (Phase 2)	20% Failed (Phase 3)	86	12	73	0	0	0	362	23	556	No	1%	0.0
23	25% Failed (Phase 2)	32% Active (Phase 3)	20% Failed (Phase 3)	46	105	73	0	15	0	362	23	625	Yes	2%	0.8
24	25% Failed (Phase 2)	14% Failed (Phase 3)	20% Failed (Phase 3)	46	66	73	0	0	0	362	23	571	No	1%	0.0
25	25% Failed (Phase 2)	55% Failed (Phase 2)	72% Active (Filing)	46	12	188	0	0	32	362	23	663	Yes	10%	5.1
26	25% Failed (Phase 2)	55% Failed (Phase 2)	8% Failed (Filing)	46	12	162	0	0	0	362	23	605	No	1%	0.0
27	25% Failed (Phase 2)	55% Failed (Phase 2)	20% Failed (Phase 3)	46	12	73	0	0	0	362	23	516	No	3%	0.0
28	50% Failed (Phase 1)	32% Active (Phase 3)	72% Active (Filing)	4	105	188	0	15	32	362	23	729	Yes	11%	5.9
29	50% Failed (Phase 1)	32% Active (Phase 3)	8% Failed (Filing)	4	105	162	0	15	0	362	23	671	Yes	1%	0.7
30	50% Failed (Phase 1)	32% Active (Phase 3)	20% Failed (Phase 3)	4	105	73	0	15	0	362	23	583	No	3%	0.0
31	50% Failed (Phase 1)	14% Failed (Phase 3)	72% Active (Filing)	4	66	188	0	0	32	362	23	676	Yes	5%	2.5
32	50% Failed (Phase 1)	14% Failed (Phase 3)	8% Failed (Filing)	4	66	162	0	0	0	362	23	618	Yes	1%	0.3
33	50% Failed (Phase 1)	14% Failed (Phase 3)	20% Failed (Phase 3)	4	66	73	0	0	0	362	23	529	No	1%	0.0
34	50% Failed (Phase 1)	55% Failed (Phase 2)	72% Active (Filing)	4	12	188	0	0	32	362	23	621	Yes	20%	10.3
35	50% Failed (Phase 1)	55% Failed (Phase 2)	8% Failed (Filing)	4	12	162	0	0	0	362	23	563	No	2%	0.0
36	50% Failed (Phase 1)	55% Failed (Phase 2)	20% Failed (Phase 3)	4	12	73	0	0	0	362	23	474	No	6%	0.0
														100%	41.7

Notes:
(1) Program Compounds either succeeded through 2003 and are still currently in development as of 4Q 2003 ("Active") or were terminated in 2001-2003 and are no longer in development as of this date ("Failed").
(2) Probabilities represent the likelihood of each drug reaching a stage of development.
(3) Actual Spending equals planned nominal spending in 2001-2003 assuming each compound's development status per scenario.
(4) Expected Spending equals forecast nominal spending multiplied by the cumulative probability of launch for each compound.
(5) ABT-594 has an assumed 100% chance of passing the FDA Filing Stage once it passes Phase 3; therefore, Active (Phase 3) is synonymous with Active (Filing).
(6) Actual spending as of 2004 Plan + Forecast Spending through 2004 for 6 other compounds.
(7) Actual spending as of 2004 Plan + Forecast Spending through 2004 for certain milestone and management fees paid to Hancock.
(8) Scenario Probability = [A] x [B] x [C]

Exhibit 9.3
LOW CASE
2003 'But-for' Annual Research Plan Scenarios

	Scenario as of Planning Period (Q4 2002)[1][2]			2001-2002 Actual Spending ($ millions)[3]		2003-2004 Expected Spending ($millions)[4]				2003 Final Plan (Other Spending)		TOTAL	Hancock 2003 Payment?	Expected Payment	
'But-for' Scenario	[A] ABT-518	[B] ABT-594	[C] ABT-773	ABT-518	ABT-594	ABT-773	ABT-518	ABT-594	ABT-773	All Other Compounds 4-year spending[5]	Milestone and Management Fees 4-year spending[6]	4-year Forecast Scenario	*if >$614m then yes*	*Scenario Probability[7]*	*Expected Payment Value*
1	19% Active (Phase 2)	20% Active (Phase 3)	75% Active (Filed)	37	73	143	25	34	68	314	23	716	Yes	3%	1.6
2	19% Active (Phase 2)	20% Active (Phase 3)	19% Failed (Filing)	37	73	162	25	34	0	314	23	668	Yes	1%	0.4
3	19% Active (Phase 2)	11% Failed (Phase 3)	75% Active (Filed)	37	66	143	25	0	68	314	23	676	Yes	2%	0.9
4	19% Active (Phase 2)	11% Failed (Phase 3)	19% Failed (Filing)	37	66	162	25	0	0	314	23	628	Yes	0%	0.2
5	56% Failed (Phase 2)	20% Active (Phase 3)	75% Active (Filed)	46	73	143	0	34	68	314	23	701	Yes	8%	4.8
6	56% Failed (Phase 2)	20% Active (Phase 3)	19% Failed (Filing)	46	73	162	0	34	0	314	23	652	Yes	2%	1.2
7	56% Failed (Phase 2)	11% Failed (Phase 3)	75% Active (Filed)	46	66	143	0	0	68	314	23	660	Yes	5%	2.8
8	56% Failed (Phase 2)	11% Failed (Phase 3)	19% Failed (Filing)	46	66	162	0	0	0	314	23	612	No	1%	0.0
9	19% Active (Phase 2)	20% Active (Phase 3)	6% Failed (Phase 3)	37	73	73	25	34	0	314	23	579	No	0%	0.0
10	19% Active (Phase 2)	11% Failed (Phase 3)	6% Failed (Phase 3)	37	66	73	25	0	0	314	23	539	No	0%	0.0
11	19% Active (Phase 2)	69% Failed (Phase 2)	75% Active (Filed)	37	12	143	25	0	68	314	23	621	Yes	10%	5.6
12	19% Active (Phase 2)	69% Failed (Phase 2)	19% Failed (Filing)	37	12	162	25	0	0	314	23	573	No	2%	0.0
13	19% Active (Phase 2)	69% Failed (Phase 2)	6% Failed (Phase 3)	37	12	73	25	0	0	314	23	484	No	1%	0.0
14	56% Failed (Phase 2)	20% Active (Phase 3)	6% Failed (Phase 3)	46	73	73	0	34	0	314	23	563	No	1%	0.0
15	56% Failed (Phase 2)	11% Failed (Phase 3)	6% Failed (Phase 3)	46	66	73	0	0	0	314	23	523	No	0%	0.0

Exhibit 9.3
LOW CASE
2003 'But-for' Annual Research Plan Scenarios

	Scenario as of Planning Period (Q4 2002)[1][2]			2001-2002 Actual Spending ($ millions)[3]		2003-2004 Expected Spending ($millions)[4]			2003 Final Plan (Other Spending)		TOTAL	Hancock 2003 Payment?	Expected Payment	
'But-for' Scenario	[A] ABT-518	[B] ABT-594	[C] ABT-773	ABT-518	ABT-594	ABT-773	ABT-518	ABT-594	ABT-773	All Other Compounds 4-year spending[5]	Milestone and Management Fees 4-year spending[6]	4-year Forecast Scenario	*if >$614m then yes*	*Scenario Probability*[7]	*Expected Payment Value*
16	56% Failed (Phase 2)	69% Failed (Phase 2)	75% Active (Filed)	46	12	143	0	0	68	314	23	606	No	29%	0.0
17	56% Failed (Phase 2)	69% Failed (Phase 2)	19% Failed (Filing)	46	12	162	0	0	0	314	23	557	No	7%	0.0
18	56% Failed (Phase 2)	69% Failed (Phase 2)	6% Failed (Phase 3)	46	12	73	0	0	0	314	23	468	No	2%	0.0
19	25% Failed (Phase 1)	20% Active (Phase 3)	75% Active (Filed)	4	73	143	0	34	68	314	23	658	Yes	4%	2.1
20	25% Failed (Phase 1)	20% Active (Phase 3)	19% Failed (Filing)	4	73	162	0	34	0	314	23	610	No	1%	0.0
21	25% Failed (Phase 1)	20% Active (Phase 3)	6% Failed (Phase 3)	4	73	73	0	34	0	314	23	521	No	0%	0.0
22	25% Failed (Phase 1)	11% Failed (Phase 3)	75% Active (Filed)	4	66	143	0	0	68	314	23	618	Yes	2%	1.3
23	25% Failed (Phase 1)	11% Failed (Phase 3)	19% Failed (Filing)	4	66	162	0	0	0	314	23	570	No	1%	0.0
24	25% Failed (Phase 1)	11% Failed (Phase 3)	6% Failed (Phase 3)	4	66	73	0	0	0	314	23	481	No	0%	0.0
25	25% Failed (Phase 1)	69% Failed (Phase 2)	75% Active (Filed)	4	12	143	0	0	68	314	23	563	No	13%	0.0
26	25% Failed (Phase 1)	69% Failed (Phase 2)	19% Failed (Filing)	4	12	162	0	0	0	314	23	515	No	3%	0.0
27	25% Failed (Phase 1)	69% Failed (Phase 2)	6% Failed (Phase 3)	4	12	73	0	0	0	314	23	426	No	1%	0.0
														100%	21.0

Notes:
(1) Program Compounds either succeeded through 2002 and are still currently in development as of 4Q 2002 ("Active") or were terminated in 2001 or 2002 and are no longer in development as of this date ("Failed").
(2) Probabilities represent the probability of each drug reaching a specific stage of development.
(3) Actual Spending equals planned nominal spending in 2001-2002 assuming the compound has not been terminated.
(4) Expected Spending equals forecasted nominal spending multiplied by the cumulative probability of launch for each compound.
(5) Actual spending as of 2003 Plan + Forecast Spending through 2004 for 6 other compounds.
(6) Actual spending as of 2003 Plan + Forecast Spending through 2004 for certain milestone and management fees paid to Hancock.
(7) Scenario Probability = [A] x [B] x [C]

Exhibit 9.4
LOW CASE
2004 'But-for' Annual Research Plan Scenarios

	Scenario as of Planning Period (Q4 2003)[1][2]			2001-2003 Actual Spending ($ millions)[3]		2004 Expected Spending ($ millions)[4]				2003 Final Plan (Other Spending)		TOTAL	Hancock 2003 Payment?	Expected Payment	
'But-for' Scenario	[A] ABT-518	[B] ABT-594	[C] ABT-773	ABT-518	ABT-594[5]	ABT-773	ABT-518	ABT-594[5]	ABT-773	All Other Compounds 4-year spending[6]	Milestone and Management Fees 4-year spending[7]	4-year Forecast Scenario	*if >$614m then yes*	*Scenario Probability*[8]	*Expected Payment Value*
1	8% Active (Phase 3)	20% Active (Phase 3)	75% Active (Filing)	72	105	188	21	15	32	352	23	807	Yes	1%	0.6
2	11% Failed (Phase 3)	20% Active (Phase 3)	75% Active (Filing)	86	105	188	0	15	32	352	23	801	Yes	2%	0.9
3	8% Active (Phase 3)	20% Active (Phase 3)	19% Failed (Filing)	72	105	162	21	15	0	352	23	749	Yes	0%	0.1
4	11% Failed (Phase 3)	20% Active (Phase 3)	19% Failed (Filing)	86	105	162	0	15	0	352	23	743	Yes	0%	0.2
5	8% Active (Phase 3)	11% Failed (Phase 3)	75% Active (Filing)	72	66	188	21	0	32	352	23	753	Yes	1%	0.3
6	11% Failed (Phase 3)	11% Failed (Phase 3)	75% Active (Filing)	86	66	188	0	0	32	352	23	747	Yes	1%	0.5
7	8% Active (Phase 3)	11% Failed (Phase 3)	19% Failed (Filing)	72	66	162	21	0	0	352	23	696	Yes	0%	0.1
8	11% Failed (Phase 3)	11% Failed (Phase 3)	19% Failed (Filing)	86	66	162	0	0	0	352	23	689	Yes	0%	0.1
9	56% Failed (Phase 2)	20% Active (Phase 3)	75% Active (Filing)	46	105	188	0	15	32	352	23	761	Yes	8%	4.3
10	56% Failed (Phase 2)	20% Active (Phase 3)	19% Failed (Filing)	46	105	162	0	15	0	352	23	703	Yes	2%	1.1
11	56% Failed (Phase 2)	11% Failed (Phase 3)	75% Active (Filing)	46	66	188	0	0	32	352	23	707	Yes	5%	2.5
12	56% Failed (Phase 2)	11% Failed (Phase 3)	19% Failed (Filing)	46	66	162	0	0	0	352	23	649	Yes	1%	0.6
13	8% Active (Phase 3)	20% Active (Phase 3)	6% Failed (Phase 3)	72	105	73	21	15	0	352	23	660	Yes	0%	0.0
14	11% Failed (Phase 3)	20% Active (Phase 3)	6% Failed (Phase 3)	86	105	73	0	15	0	352	23	654	Yes	0%	0.1
15	8% Active (Phase 3)	11% Failed (Phase 3)	6% Failed (Phase 3)	72	66	73	21	0	0	352	23	607	No	0%	0.0

Exhibit 9.4
LOW CASE
2004 'But-for' Annual Research Plan Scenarios

	Scenario as of Planning Period (Q4 2003)[1][2]			2001-2003 Actual Spending ($ millions)[3]		2004 Expected Spending ($ millions)[4]				2003 Final Plan (Other Spending)		TOTAL	Hancock 2003 Payment?	Expected Payment	
'But-for' Scenario	[A] ABT-518	[B] ABT-594	[C] ABT-773	ABT-518	ABT-594[5]	ABT-773	ABT-518	ABT-594[5]	ABT-773	All Other Compounds 4-year spending[6]	Milestone and Management Fees 4-year spending[7]	4-year Forecast Scenario	*if >$614m then yes*	*Scenario Probability*[8]	*Expected Payment Value*
16	11% Failed (Phase 3)	11% Failed (Phase 3)	6% Failed (Phase 3)	86	56	73	0	0	0	352	23	600	No	0%	0.0
17	8% Active (Phase 3)	69% Failed (Phase 2)	75% Active (Filing)	72	12	188	21	0	32	352	23	699	Yes	4%	2.0
18	11% Failed (Phase 3)	69% Failed (Phase 2)	75% Active (Filing)	86	12	188	0	0	32	352	23	693	Yes	6%	3.0
19	8% Active (Phase 3)	69% Failed (Phase 2)	19% Failed (Filing)	72	12	162	21	0	0	352	23	641	Yes	1%	0.5
20	11% Failed (Phase 3)	69% Failed (Phase 2)	19% Failed (Filing)	86	12	162	0	0	0	352	23	635	Yes	1%	0.8
21	8% Active (Phase 3)	69% Failed (Phase 2)	6% Failed (Phase 3)	72	12	73	21	0	0	352	23	552	No	0%	0.0
22	11% Failed (Phase 3)	69% Failed (Phase 2)	6% Failed (Phase 3)	86	12	73	0	0	0	352	23	546	No	0%	0.0
23	56% Failed (Phase 2)	20% Active (Phase 3)	6% Failed (Phase 3)	46	105	73	0	15	0	352	23	614	Yes	1%	0.3
24	56% Failed (Phase 2)	11% Failed (Phase 3)	6% Failed (Phase 3)	46	66	73	0	0	0	352	23	560	No	0%	0.0
25	56% Failed (Phase 2)	69% Failed (Phase 2)	75% Active (Filing)	46	12	188	0	0	32	352	23	653	Yes	29%	15.2
26	56% Failed (Phase 2)	69% Failed (Phase 2)	19% Failed (Filing)	46	12	162	0	0	0	352	23	595	No	7%	0.0
27	56% Failed (Phase 2)	69% Failed (Phase 2)	6% Failed (Phase 3)	46	12	73	0	0	0	352	23	506	No	2%	0.0
28	25% Failed (Phase 1)	20% Active (Phase 3)	75% Active (Filing)	4	105	188	0	15	32	352	23	719	Yes	4%	1.9
29	25% Failed (Phase 1)	20% Active (Phase 3)	19% Failed (Filing)	4	105	162	0	15	0	352	23	661	Yes	1%	0.5
30	25% Failed (Phase 1)	20% Active (Phase 3)	6% Failed (Phase 3)	4	105	73	0	15	0	352	23	572	No	0%	0.0

Exhibit 9.4
LOW CASE
2004 'But-for' Annual Research Plan Scenarios

	Scenario as of Planning Period (Q4 2003)[1][2]			2001-2003 Actual Spending ($ millions)[3]		2004 Expected Spending ($ millions)[4]			2003 Final Plan (Other Spending)		TOTAL	Hancock 2003 Payment?	Expected Payment	
'But-for' Scenario	[A] ABT-518	[B] ABT-594	[C] ABT-773	ABT-518	ABT-594[5]	ABT-773	ABT-518	ABT-594[5]	ABT-773	All Other Compounds 4-year spending[6]	Milestone and Management Fees 4-year spending[7]	4-year Forecast Scenario	*if >$614m then yes*	*Scenario Probability[8]*	*Expected Payment Value*
31	25% Failed (Phase 1)	11% Failed (Phase 3)	75% Active (Filing)	4	66	188	0	0	32	352	23	665	Yes	2%	1.1
32	25% Failed (Phase 1)	11% Failed (Phase 3)	19% Failed (Filing)	4	66	162	0	0	0	352	23	607	No	1%	0.0
33	25% Failed (Phase 1)	11% Failed (Phase 3)	6% Failed (Phase 3)	4	66	73	0	0	0	352	23	518	No	0%	0.0
34	25% Failed (Phase 1)	69% Failed (Phase 2)	75% Active (Filing)	4	12	188	0	0	32	352	23	610	No	13%	0.0
35	25% Failed (Phase 1)	69% Failed (Phase 2)	19% Failed (Filing)	4	12	162	0	0	0	352	23	552	No	3%	0.0
36	25% Failed (Phase 1)	69% Failed (Phase 2)	6% Failed (Phase 3)	4	12	73	0	0	0	352	23	464	No	1%	0.0
														100%	36.8

Notes:
(1) Program Compounds either succeeded through 2003 and are still currently in development as of 4Q 2003 ("Active") or were terminated in 2001-2003 and are no longer in development as of this date ("Failed").
(2) Probabilities represent the likelihood of each drug reaching a stage of development.
(3) Actual Spending equals planned nominal spending in 2001-2003 assuming each compound's development status per scenario.
(4) Expected Spending equals forecast nominal spending multiplied by the cumulative probability of launch for each compound.
(5) ABT-594 has an assumed 100% chance of passing the FDA Filing Stage once it passes Phase 3; therefore, Active (Phase 3) is synonymous with Active (Filing).
(6) Actual spending as of 2004 Plan + Forecast Spending through 2004 for 6 other compounds.
(7) Actual spending as of 2004 Plan + Forecast Spending through 2004 for certain milestone and management fees paid to Hancock.
(8) Scenario Probabilty = [A] x [B] x [C]

Exhibit 10.1

2002 Expected Spending Forecast by Program Compound
Assuming ABT-773 is Forecast to be Terminated in 4Q 2002
(November 26, 2001)
($millions)

Program Compound	Actual[1] 2001	Forecast[2] 2002-2004	Totals
Misrepresented Program Compounds			
ABT-518	2.4	-	2.4
ABT-594	5.5	-	5.5
ABT-773[3]	59.7	13.2	72.9
Subtotal	*67.6*	*13.2*	*80.8*
Other Portfolio Compounds			
ABT-510	7.2	56.1	63.3
ABT-751	5.3	43.9	49.3
ABT-627	28.7	103.2	131.9
ABT-100	7.5	38.0	45.5
ABT-724	6.6	28.4	35.1
ABT-492	20.1	124.0	144.1
Subtotal	*75.5*	*393.7*	*469.2*
Management Fees / Milestones to Huncock	-	10.0	*10.0*
Other	2.2	6.8	*9.0*
Subtotal	*2.2*	*16.8*	*19.0*
Aggregate Nominal Spending	145.3	423.7	569.0

Note:
(1) Abbott Laboratories' Amended Responses and Objections to Plaintiffs' Second Set of Interrogatories, August 3, 2007, Response #15. 2001 Spending is pro-rated to the March 31-December 31 Program Term on a daily basis.
(2) See 2002 Research Plan (ABBT 0004521- 0004535). Nominal spending is adjusted by probability of success and potential ramp-down costs in the event of termination.
(3) ABT-773 Forecast Expected Spending is assumed to equal to 100% of Actual Spending in 2002-2004.

PLs' RP

CMR International Success Rates

Peter Joshua and Cyndy Lumley 14th April 2004

Agenda

- Success Rates Methodologies
  - Longitudinal analysis
  - CMR Methodology: By year of entry into phase
  - Progression-Decision Methodology: By year of decision to progress or terminate
- Understanding the data and trends
- Focus on Terminations

Part 1 - Methodologies for calculating success rates

Methodologies

- Longitudinal analysis
- CMR Methodology: By year of entry into phase
- Progression-Decision Methodology: By year of decision to progress or terminate

Success rates to market: longitudinal study of NASs entering man 1994-95

NASs first tested in man in 1994/95	Status at the end of 2002					
	Phase I	Phase II	Phase III	Reg review	Launched	Terminated
155	1	4	8	8	16	118

Outcome

16 NASs Launched
118 NASs Terminated
21 NASs Still in Development

Success rate for NASs first tested in man 1994/95, with known outcome

= (16/134)*100
= 12%

Range of possible success rates, for NASs first tested in man 1994/95, taking into account those with unknown outcome

= (16/155)*100 = 10% TO = (34/155)*100 = 22%

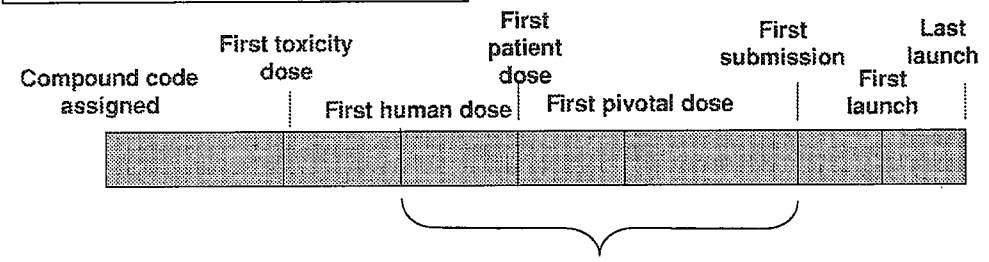
Source: CMR International Unaudited data Confidential Slide No 5

CMR Methodology: By year of entry into phase

- Calculates real 'between phase' success rates
- Based on year of entry into phase
- Multiplies 'between phase' success rates to obtain a probability of success to market from each phase

CMR Methodology
Data source: CMR R&D cycle times database

>1800 new active substances
(NASs)
In active development 1994-2003
50 companies



Clinical Development

Source: CMR International | Unaudited data | Confidential | Slide No 7

CMR Methodology: Calculating success rates by phase

- Calculate success rates for individual phases
- For example:
  - To calculate success rate for phase I, consider all NASs that entered phase I between 1997-1999 (320).
  - Three possible outcomes for those NASs by the end of 2002:
    - progressed to start of phase II (186)
    - terminated whilst in phase I (109)
    - still in phase I at the end of 2002 (25)

CMR Methodology: Calculating success rates by phase

CMR International
Perspective ● Insight ● Opinion

$$\text{Current success rate} = \frac{\text{NASs progressed}}{\text{NASs entered phase - NASs of unknown fate}} \times 100$$

$$= \frac{186}{320 - 30} \times 100 = 63\%$$

$$\text{Maximum success rate} = \frac{\text{NASs progressed + NASs of unknown fate}}{\text{NASs entered phase}} \times 100$$

$$= 66\%$$

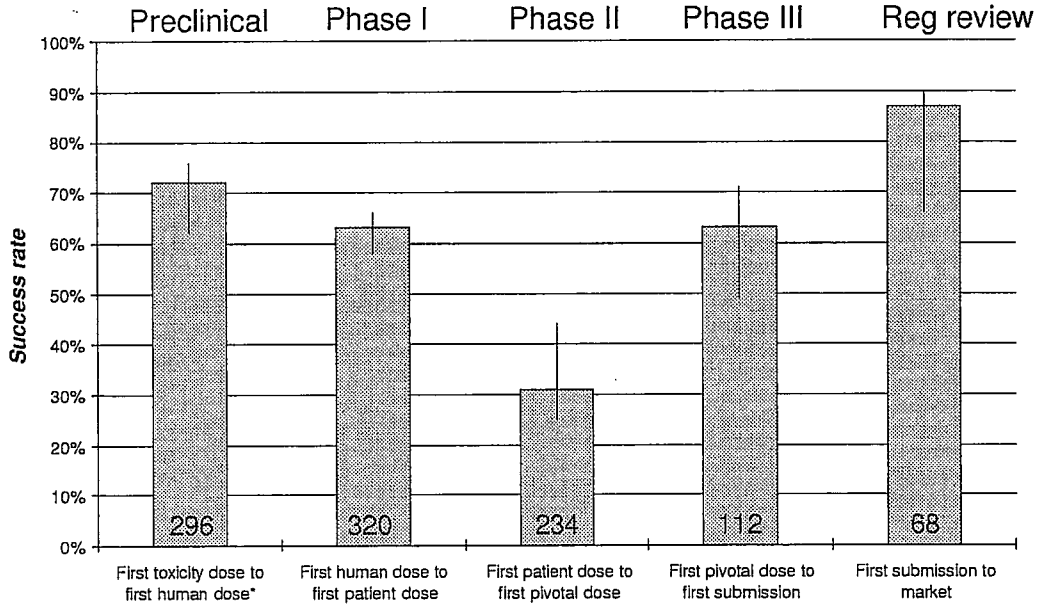
$$\text{Minimum success rate} = \frac{\text{NASs progressed}}{\text{NASs entered phase}} \times 100$$

$$= 58\%$$

Source: CMR International | Unaudited data | Confidential | Slide No. 9

Success rates between phases

(based on NASs entering phase between 1997 and 1999)

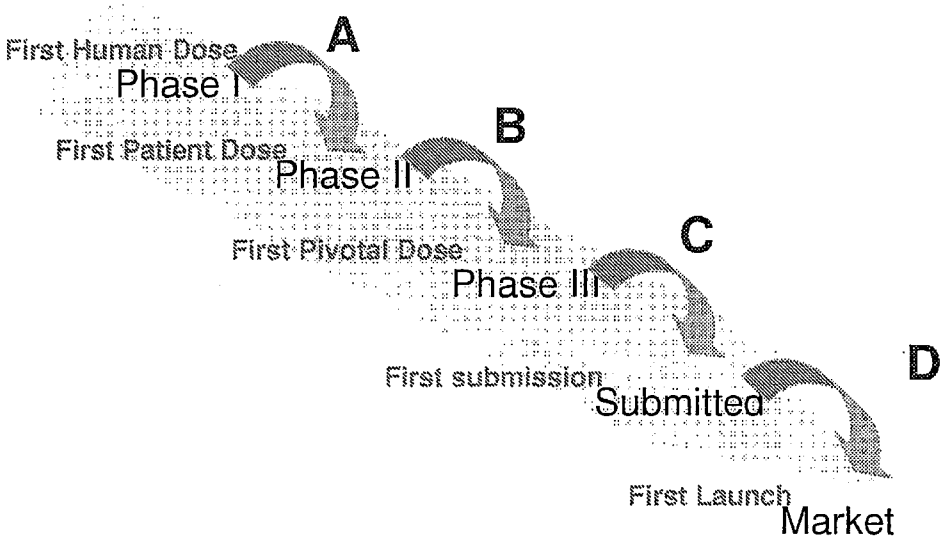


*based on NASs entering phase 99-00

High-low lines represent range of possible success rates

Source: CMR International | Unaudited data | Confidential | Slide No 10

Calculating Probabilities of Success to Market

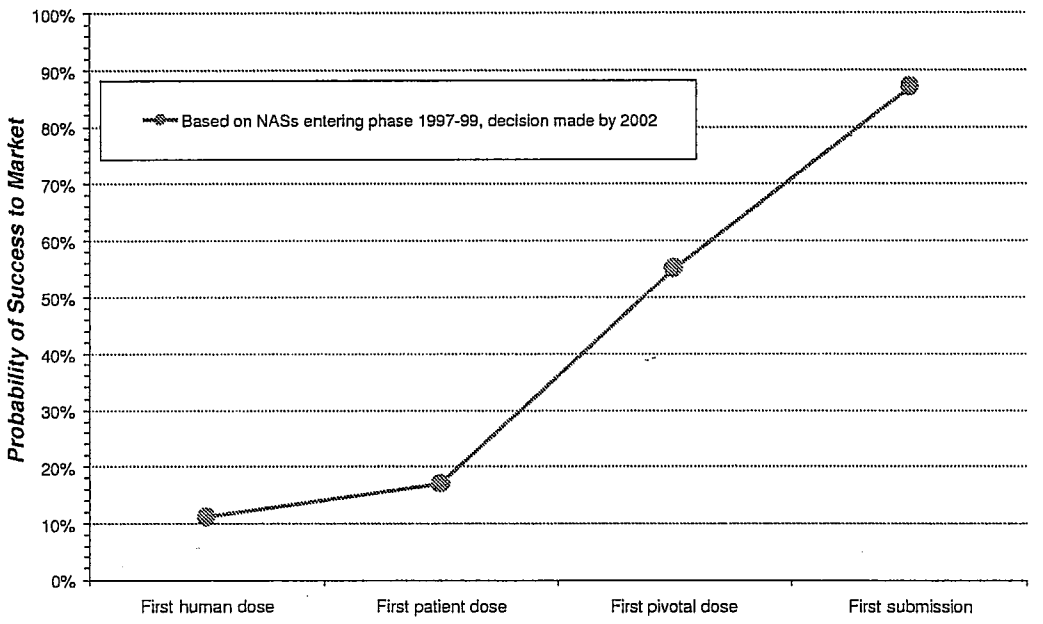


Cumulative success rate to market = ((A x B) x C) x D

where A, B, C, D = success rates between phase

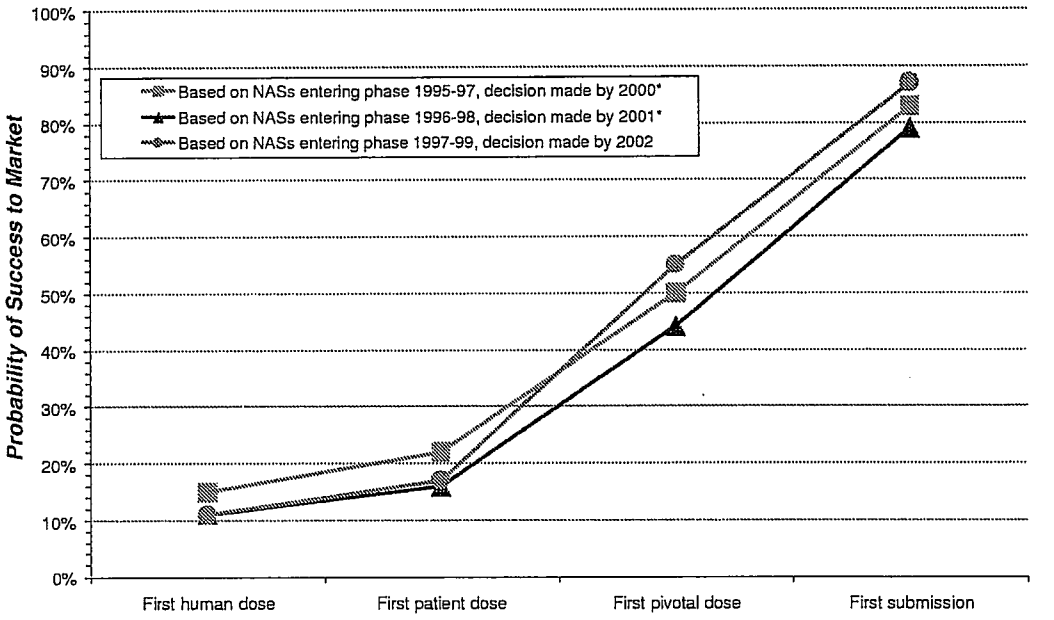
Unaudited data Confidential AT1-10001 Slide No. 11 15/10/01

Cumulative probabilities of success rates to market



Source: CMR International | Unaudited data | Confidential | Slide No. 12

Cumulative probabilities of success to market: changes over time



*as published in Ashton and Joshua (2002)

Source: CMR International | Unaudited data | Confidential | Slide No. 13

Success rates to market: longitudinal study of NASs entering man 1994-95

NASs first tested in man in 1994/95	Status at the end of 2002					
	Phase I	Phase II	Phase III	Reg review	Launched	Terminated
155	1	4	8	8	16	118
Probability of reaching market	*0.11*	*0.17*	*0.55*	*0.87*	*N/A*	*0*
*Number predicted to reach market**	*0.1*	*0.7*	*4.4*	*7.0*	*(16)*	
			12.2			

Likely success rate for NASs first tested in man 1994/95 = ((12+16)/155)*100 = 18%

**as calculated by CMR International based on NASs entering phase 1997-99*

Source: CMR International | Unaudited data | Confidential | Slide No. 14

Decision-Progression Methodology: By year of Decision

- Calculates the proportion of decisions made that were to progress the NAS
- Based on year of decision (irrespective of when the NAS entered the phase)
- Multiplies the proportion of progression decisions in each phase to obtain a probability of success to market

Decision-Progression Methodology: Calculating success rates by date of decision

- Calculate proportion of progression decisions for individual phases
- For example:
  - To calculate progression decisions for phase I, consider all NASs that were in Phase I and for which a decision was made to terminate or progress between 2000-2002 (286).
  - Two possible outcomes for those NASs:
    - progressed to start of phase II (163)
    - terminated whilst in phase I (123)

Progression-Decision Methodology: By date of decision

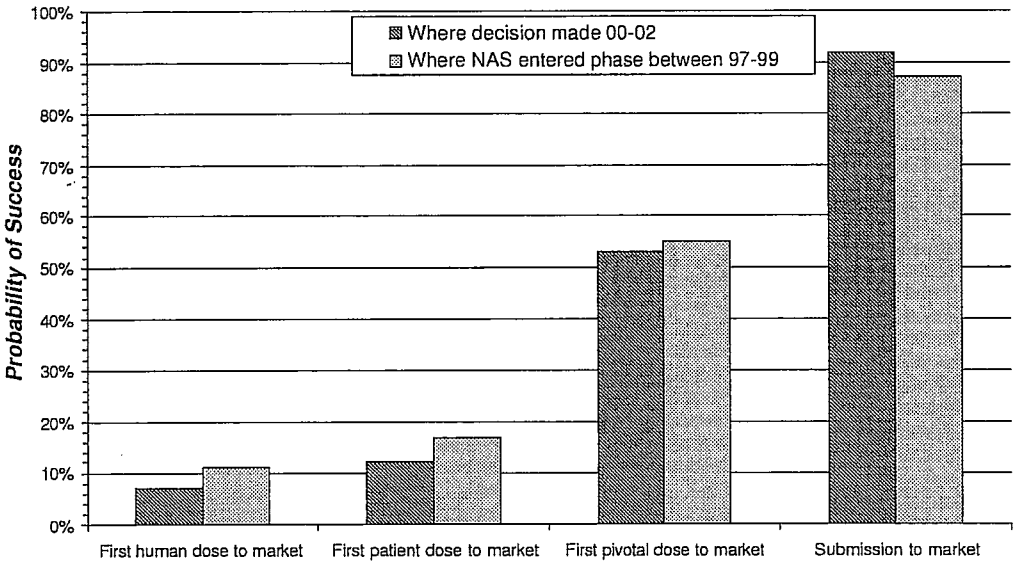
CMR International
Perspective ● Insight ● Opinion

$$\text{Proportion of progression decisions following first human dose} = \frac{\text{NASs progressed to first patient dose}}{\text{NASs progressed} + \text{NASs terminated}}$$

$$= \frac{163}{163+123} \times 100 = 57\%$$

Source: CMR International | Unaudited data | Confidential | Slide No.

Current probabilities of success rates to market



Source: CMR International | Unaudited data | Confidential | Slide No. 18

Summary

Year of entry into phase	Year of decision	Longitudinal analysis
Based on real between phase success rates	Based on decisions made in a given time period	Real
Current – based on defined year of entry	Current with respect to decision making, but no limit on year of entry to phase	Historical
Gives insight into changes in fate of NASs entering phase over time	Gives insight into changes in decision making practices over time	
Takes account of NASs of unknown fate	Does not take account of NASs of unknown fate	

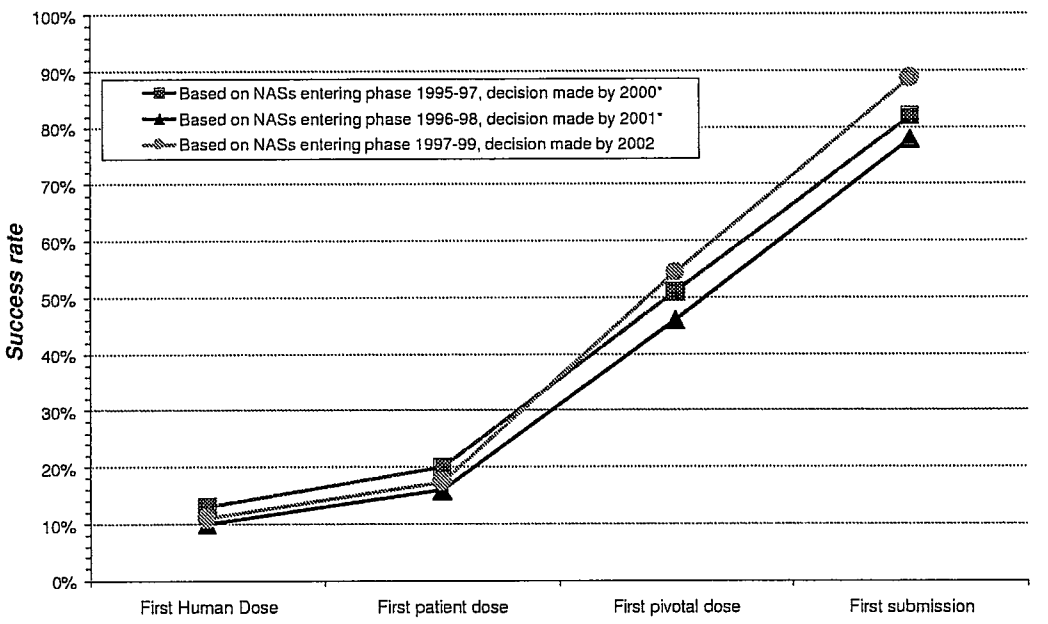
Source: CMR International Unaudited data Confidential Slide No. 19

Part 2 - Understanding the data and trends

Hypothesis 1.

- All the new technologies implemented to improve success rates (by improving candidate selection) have been counterbalanced by the increased hurdles from the market and regulatory authorities.

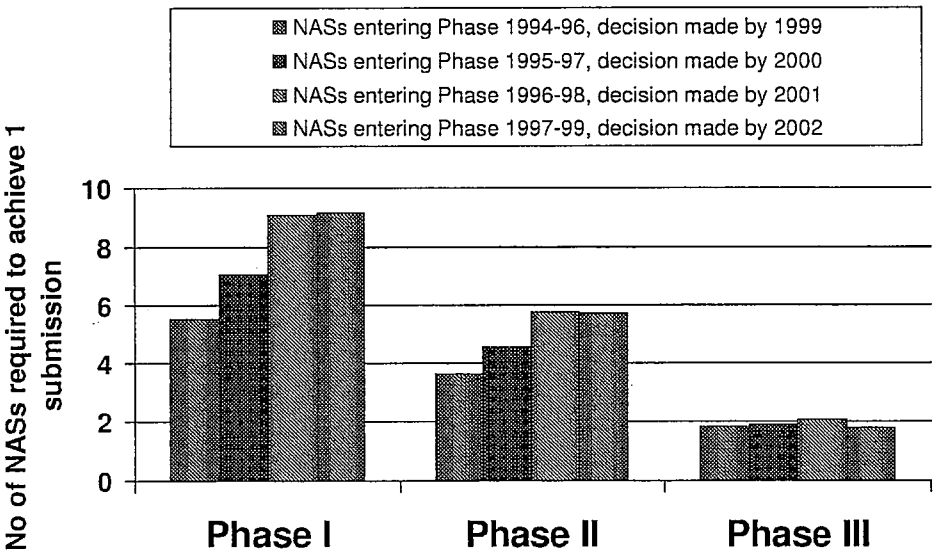
Cumulative success rates to market: changes over time for major companies



*as published in Ashton and Joshua (2002)

Source: CMR International | Unaudited data | Confidential | Slide No. 22

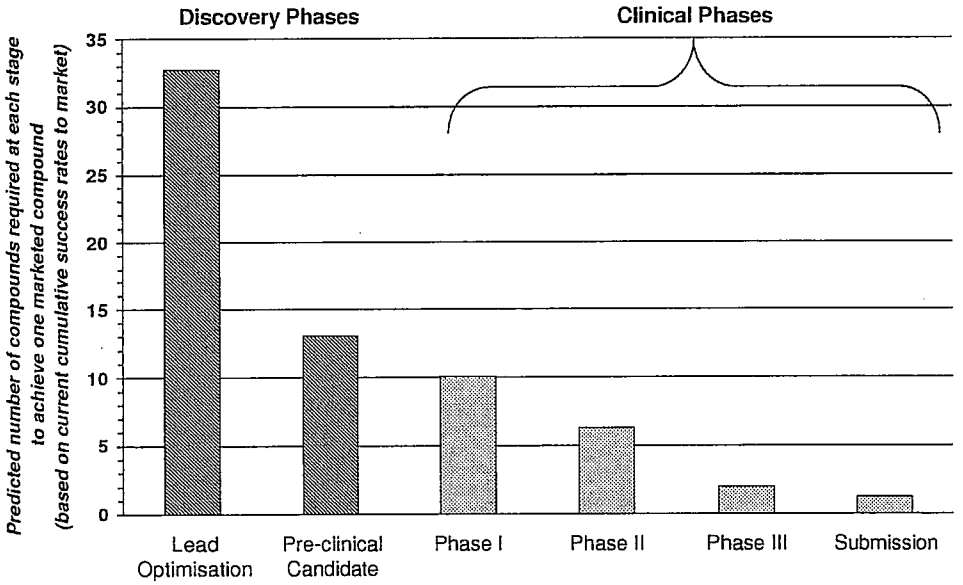
Number of NASs required in each clinical phase to achieve one submission (Major Companies)



Based on success rates calculated for NASs entering phase in each time period

Source: CMR International | Unaudited data | Confidential | Slide No. 23

How many compounds need to be investigated in each phase, in order to achieve one marketed compound (all companies)?



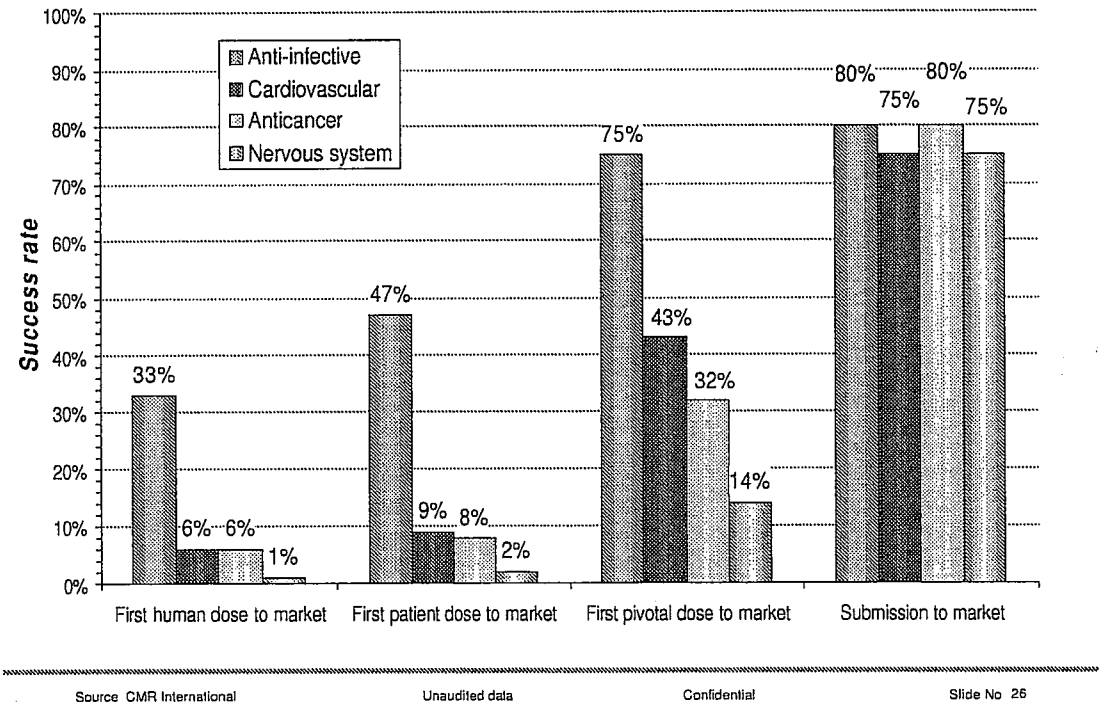
The data set used for Drug Discovery phases was those projects that entered a phase in 2000, where the fate was known by 2002. The data set used for clinical phases was based on NASs entering phase 1997-99, where a decision was made by 2002.

Source: CMR International | Unaudited data | Confidential | Slide No. 24

Hypotheses 2-4

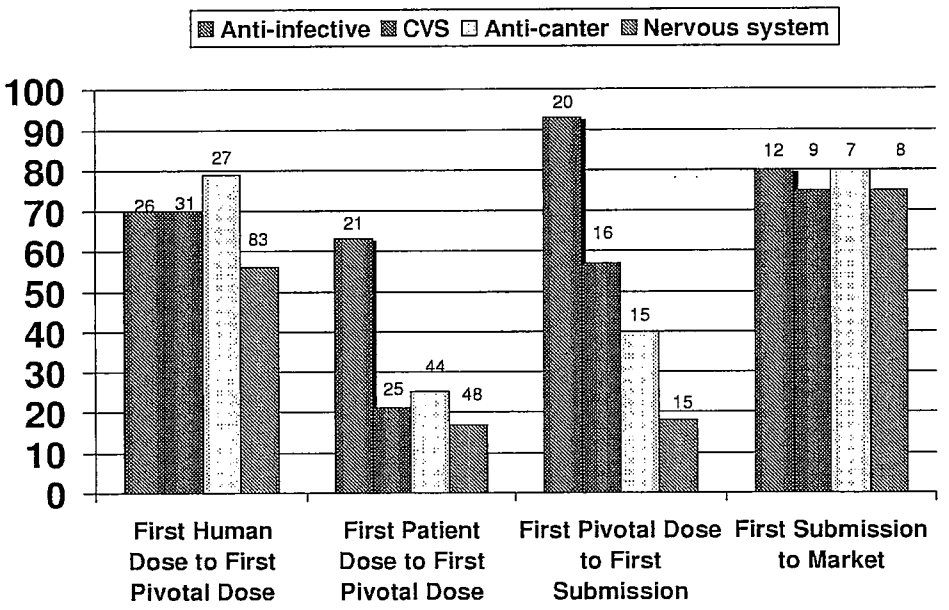
- Clinical 'proof of concept' in Phase II is critical to late stage success rates. This is easier to achieve in certain therapeutic areas, e.g. anti-infectives.
- It is more difficult to achieve success in therapy areas such as CVS where there is more commercial pressure due to the broad spectrum of treatments available
- It is a 'myth' that oncology marketing applications can be made with Phase II data only.

Cumulative success rates to market by therapeutic area



Source CMR International | Unaudited data | Confidential | Slide No 26

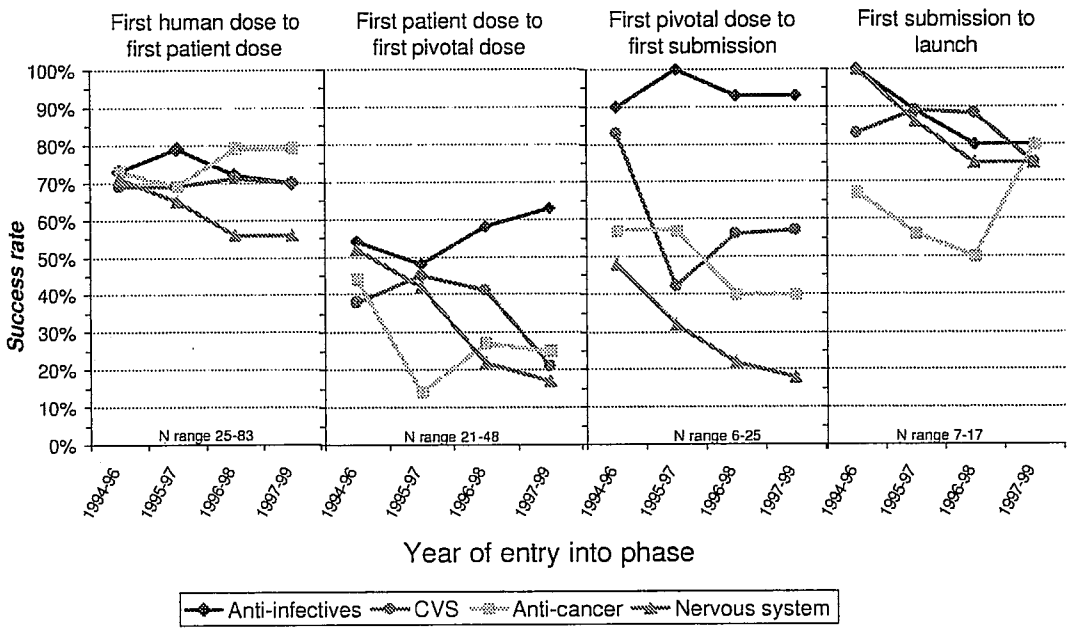
Between Phase Success Rates by Therapy Area



Based on NASs entering Phase between 1997 and 1999; decision made by end of 2002

Source: CMR International | Unaudited data | Confidential | Slide No. 27

Trends in success rates by phase and therapy area

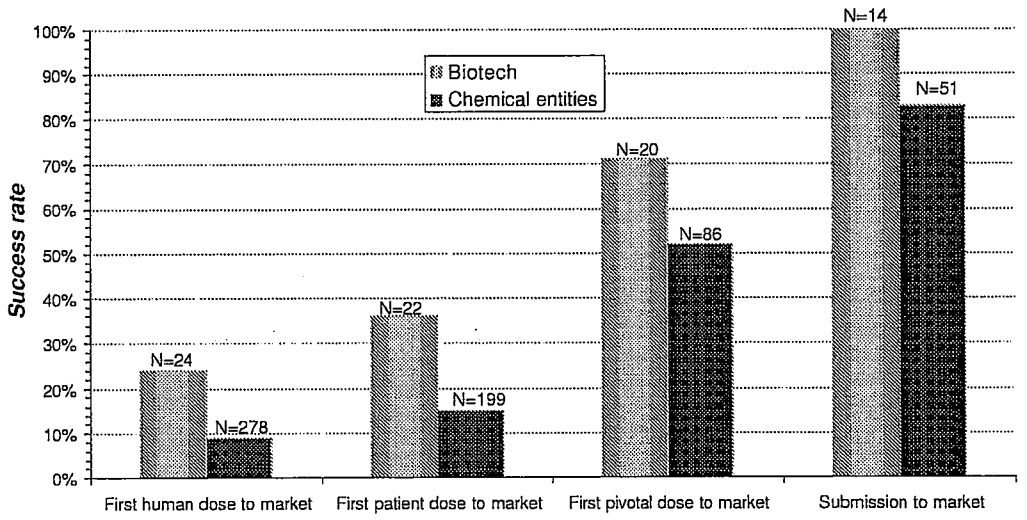


Source CMR International | Unaudited data | Confidential | Slide No. 28

Hypotheses 5-6

- Medium sized companies are responsible for developing a larger proportion of the biotech compounds,
- The commercial attractiveness of biotech products is greater for medium than for large companies.

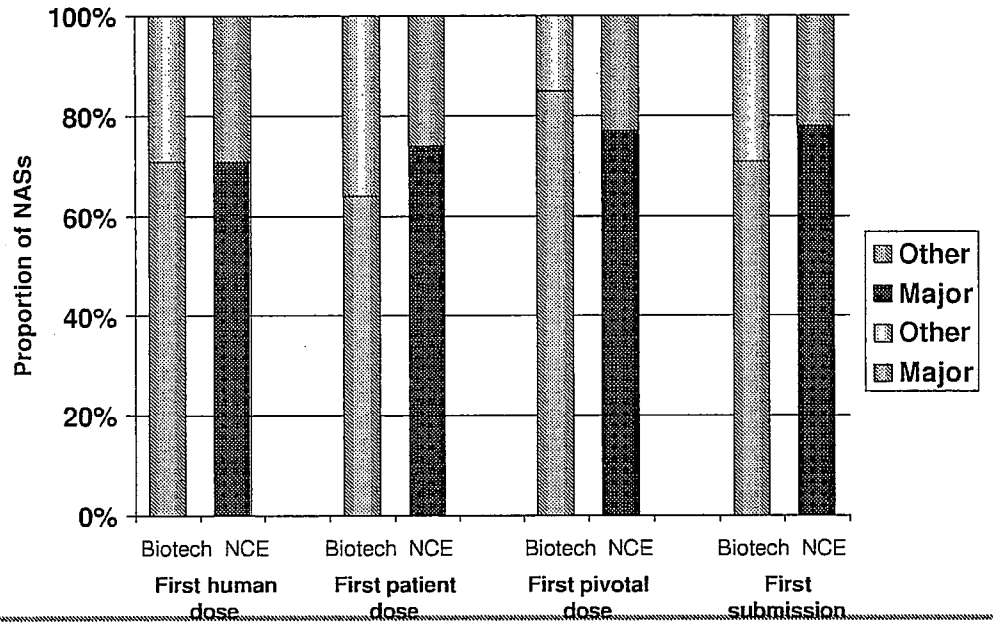
Cumulative success rates to market by product type



Based on NASs entering Phase between 1997 and 1999; decision made by end of 2002 . N=number of NASs entering each phase.

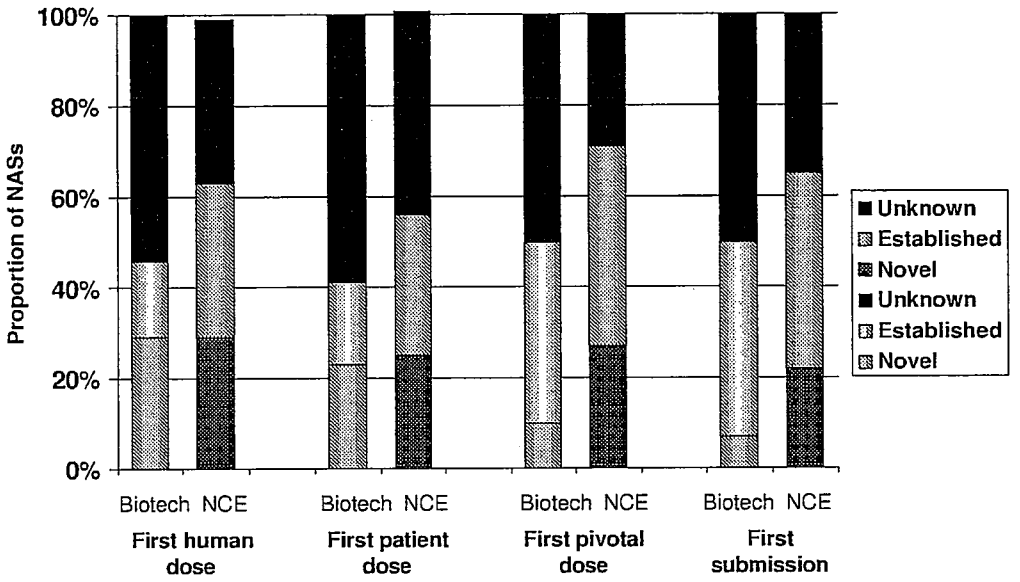
Source: CMR International | Unaudited data | Confidential | Slide No 30

Involvement of Major and Other companies in biotech and small molecule NASs



Source: CMR International Unaudited data Confidential Slide No 31

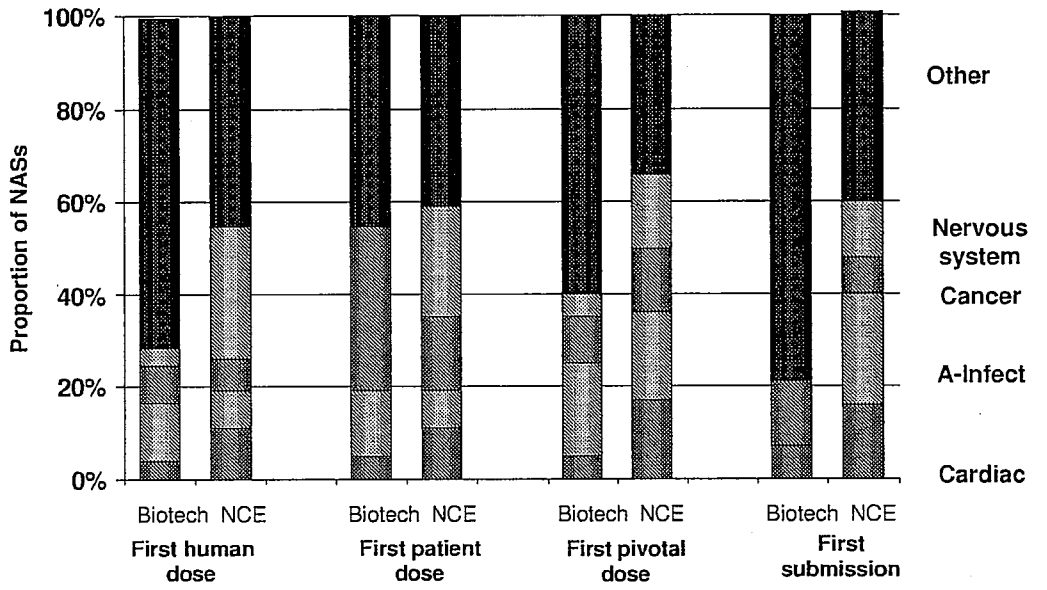
Novelty of biotech and small molecule NASs



Based on NASs entering Phase between 1997 and 1999; decision made by end of 2002.

Source: CMR International | Unaudited data | Confidential | Slide No 32

Therapy Area of biotech and small molecule NASs



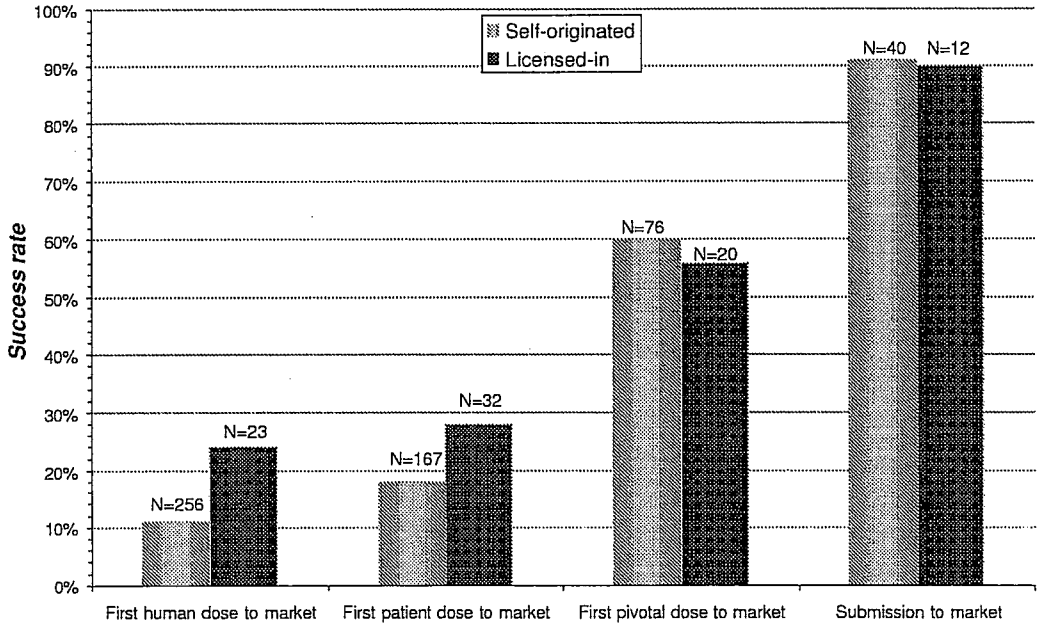
Based on NASs entering Phase between 1997 and 1999; decision made by end of 2002.

Source: CMR International Unaudited data Confidential Slide No. 33

Hypothesis 7

- Licensed in compounds have higher success rates at earlier stages because the licensee often repeats the work for the phase in which the compound was licensed in.

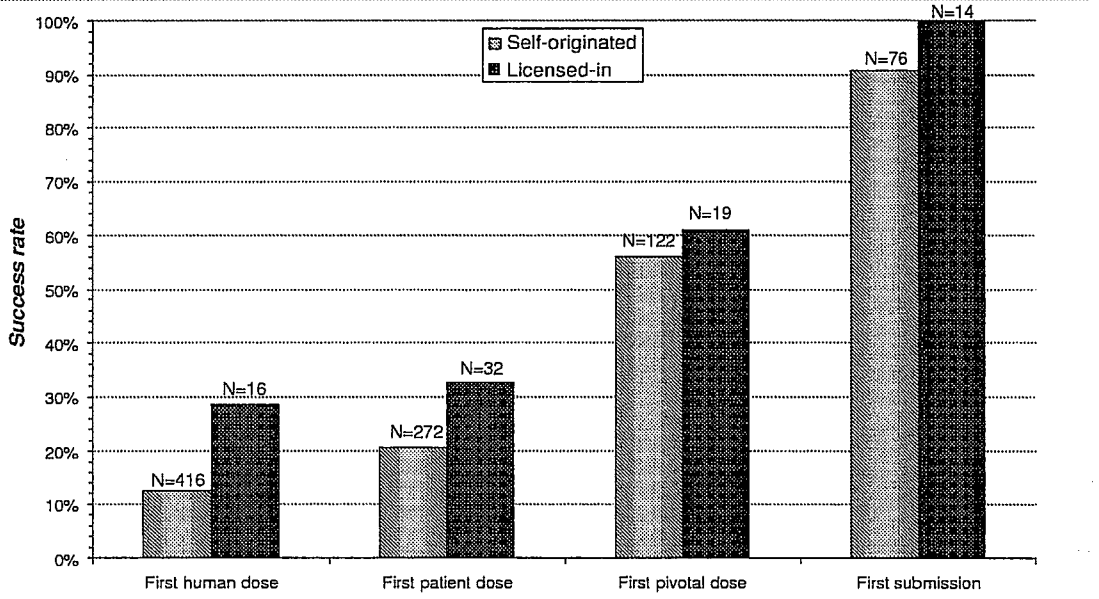
Cumulative success rates to market by origin (1)



Based on NASs entering Phase between 1997 and 1999; decision made by end of 2002 . N=number of NASs entering each phase.

Source: CMR International | Unaudited data | Confidential | Slide No 35

Cumulative success rates to market by origin (2)



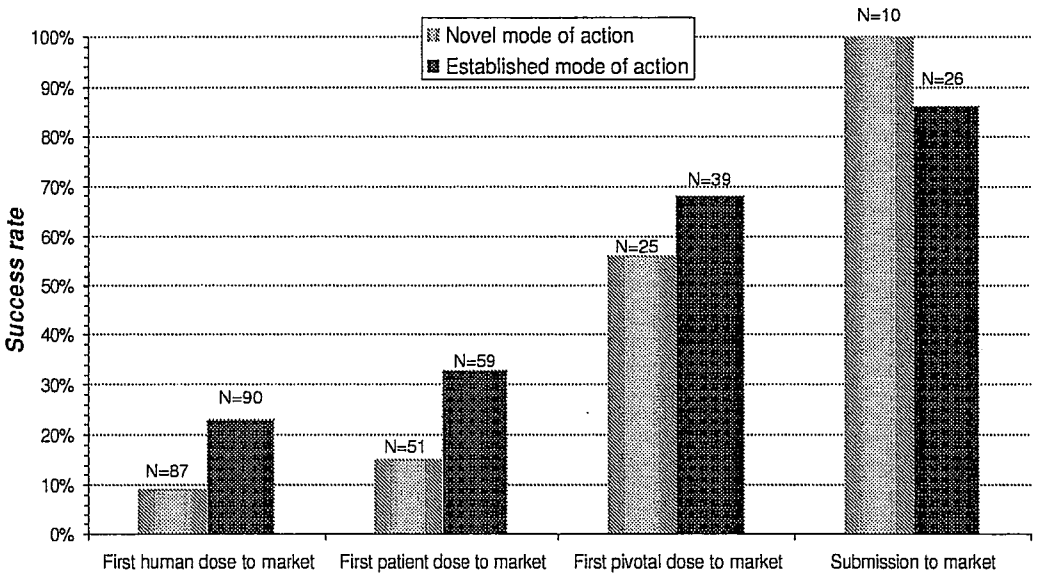
Based on NASs entering Phase between 1995 and 1999; decision made by end of 2002
Licensed in success rates calculated for the phase after licensing. N=number of NASs entering each phase.

Source: CMR International | Unaudited data | Confidential | Slide No 36

Hypotheses 8-9

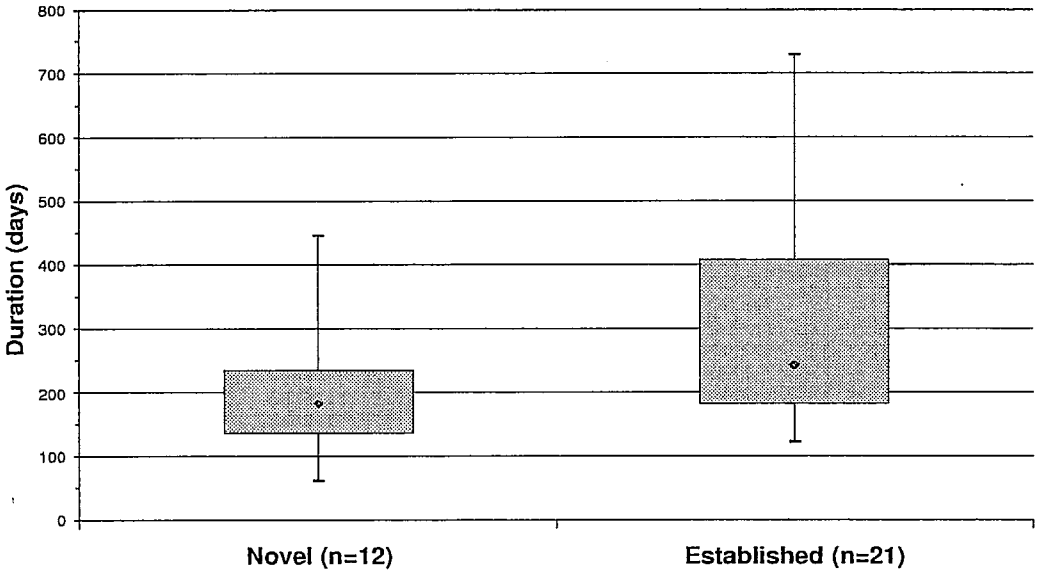
- Compounds with a 'novel' mechanism of action are more likely to achieve marketing approval than those with an 'established' mechanism of action, but the review time takes longer
- A larger number of 'novel' compounds is required in Phase 1 to achieve the same output as 'established' compounds in terms of launches

Cumulative success rates to market by mode of action



Source: CMR International | Unaudited data | Confidential | Slide No. 38

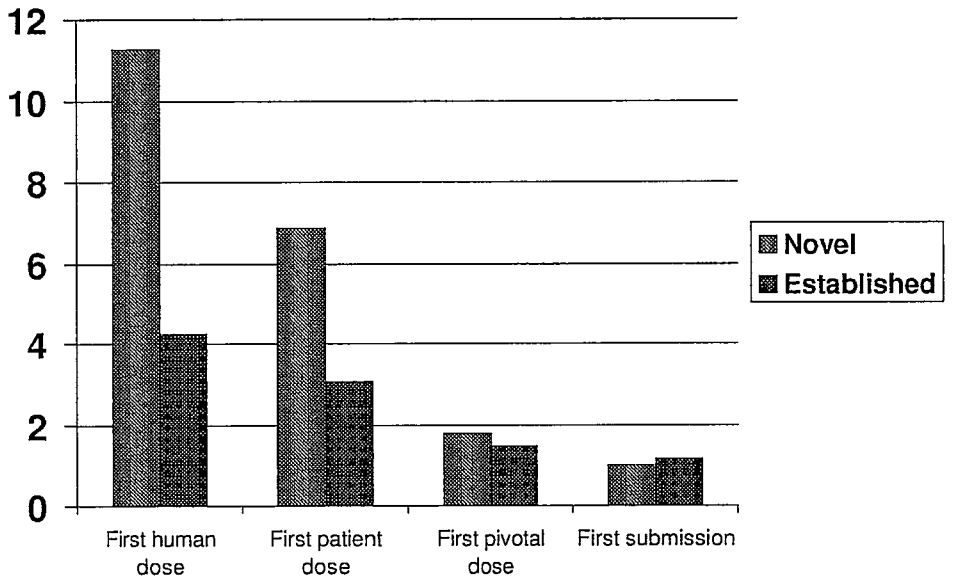
Time from 'First submission' to 'First approval' for NASs with established or novel mode of action



Based on NASs submitted between 1997 and 1999 and reaching first approval by end of 2002

Source: CMR International | Unaudited data | Confidential | Slide No 39

Numbers of NASs required in each phase to achieve 1 launch, for novel vs established mechanism of action

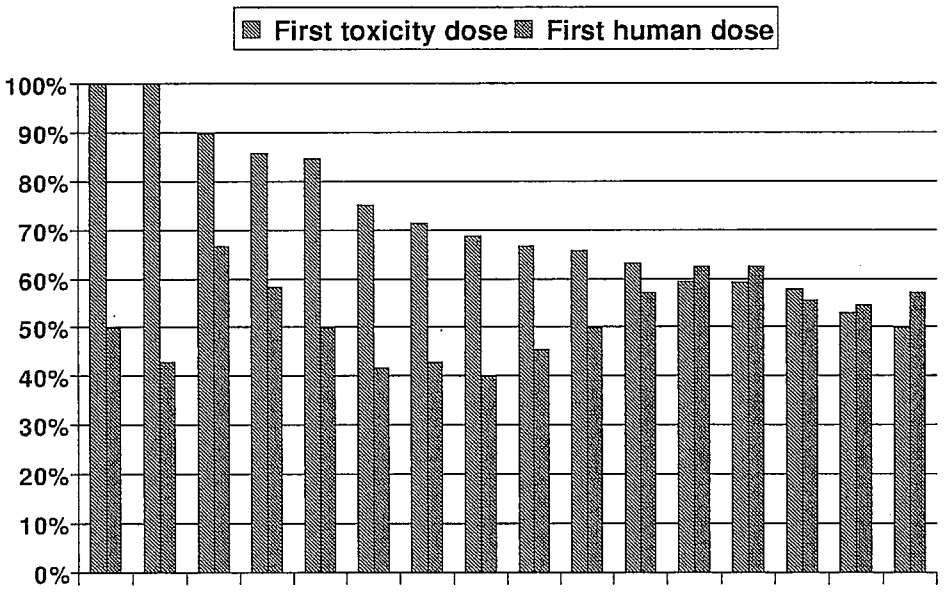


Source: CMR International | Unaudited data | Confidential | Slide No 40

Hypothesis 10

- Preclinical and Phase I have differing attrition profiles across companies, reflecting differences in strategic approach: taking high numbers into Phase I versus early attrition.

Preclinical and Phase I between phase success rates for individual companies



Based on NASs entering phase between 1999 and 2001; decision reached by end of 2002

Hypothesis 11.

CMR International
Perspective ● Insight ● Opinion

- Improving late phase attrition will have the largest single impact on future output.

Industry Statistics 2002: 34 companies

- Pipeline numbers
  - Phase I: 213
  - Phase II: 165
  - Phase III: 52
  - Submission: 45
- Success rates between phases
  - Phase I to II: 63%
  - Phase II to III: 31%
  - Phase III to Sub.: 63%
  - Sub to Launch: 87%
- Time in phase
  - Phase I: 1.63 yr
  - Phase II: 2.32 yr
  - Phase III: 2.58 yr
  - Submission: 1.21 yr

0.45 NASs per year per company

Source: CMR International | Unaudited data | Confidential | Slide No 44

Industry Statistics 2002: 14 Major companies

- Pipeline numbers
  - Phase I: 157
  - Phase II: 111
  - Phase III: 32
  - Submission: 32
- Success rates between phases
  - Phase I to II: 63%
  - Phase II to III: 32%
  - Phase III to Sub: 61%
  - Sub to Launch: 87%
- Time in phase
  - Phase I: 1.61 yr
  - Phase II: 2.32 yr
  - Phase III: 2.45 yr
  - Submission: 1.21 yr

0.76 NASs per year per company

Source: CMR International | Unaudited data | Confidential | Slide No 45

Effect of improving success rates on predicted output of Major companies

Phase I	Phase II	Phase III	Submission	OUTPUT
63%	32%	61%	87%	0.76

Source: CMR International | Unaudited data | Confidential | Slide No 46

Effect of improving success rates on predicted output of Major companies

Phase I	Phase II	Phase III	Submission	OUTPUT
63%	32%	61%	87%	0.76
75%	32%	61%	87%	0.79

Source: CMR International | Unaudited data | Confidential | Slide No. 47

Effect of improving success rates on predicted output of Major companies

Phase I	Phase II	Phase III	Submission	OUTPUT
63%	32%	61%	87%	0.76
75%	32%	61%	87%	0.79
63%	55%	61%	87%	1.02

Source: CMR International | Unaudited data | Confidential | Slide No. 48

Effect of improving success rates on predicted output of Major companies

Phase I	Phase II	Phase III	Submission	OUTPUT
63%	32%	61%	87%	0.76
75%	32%	61%	87%	0.79
63%	55%	61%	87%	1.02
63%	32%	90%	87%	0.99

Effect of improving success rates on predicted output of Major companies

Phase I	Phase II	Phase III	Submission	OUTPUT
63%	32%	61%	87%	0.76
75%	32%	61%	87%	0.79
63%	55%	61%	87%	1.02
63%	32%	90%	87%	0.99
63%	32%	61%	100%	0.87

Source: CMR International Unaudited data Confidential Slide No 50

Effect of improving success rates on predicted output of Major companies

Phase I	Phase II	Phase III	Submission	OUTPUT
63%	32%	61%	87%	0.76
75%	32%	61%	87%	0.79
63%	55%	61%	87%	1.02
63%	32%	90%	87%	0.99
63%	32%	61%	100%	0.87
63%	32%	90%	100%	1.14

Source: CMR International Unaudited data Confidential Slide No. 51

Effect of improving success rates on predicted output of Major companies

Phase I	Phase II	Phase III	Submission	OUTPUT
63%	32%	61%	87%	0.76
75%	32%	61%	87%	0.79
63%	55%	61%	87%	1.02
63%	32%	90%	87%	0.99
63%	32%	61%	100%	0.87
63%	32%	90%	100%	1.14
63%	55%	90%	100%	1.55

Source: CMR International Unaudited data Confidential Slide No. 52

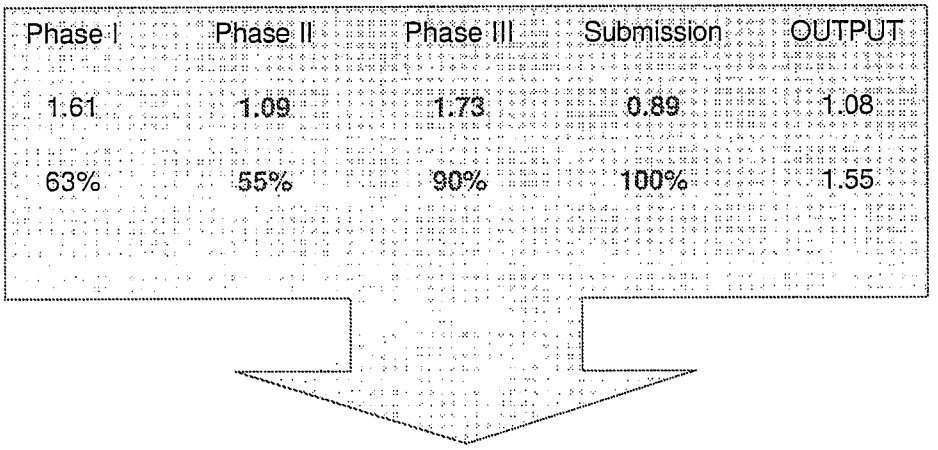
Effect of improving cycle times on predicted output of Major companies

CMR International
Perspective ● Insight ● Opinion

Phase I	Phase II	Phase III	Submission	OUTPUT
1.61	2.32	2.45	1.21	0.76
0.61	2.32	2.45	1.21	0.87
1.61	1.09	2.45	1.21	0.9
1.61	2.32	1.73	1.21	0.84
1.61	2.32	2.45	0.89	0.79
1.61	2.32	1.73	0.89	0.88
1.61	1.09	1.73	0.89	1.08

Source: CMR International Unaudited data Confidential Slide No. 53

Effect of improving success rates and cycle times on predicted output of Major companies

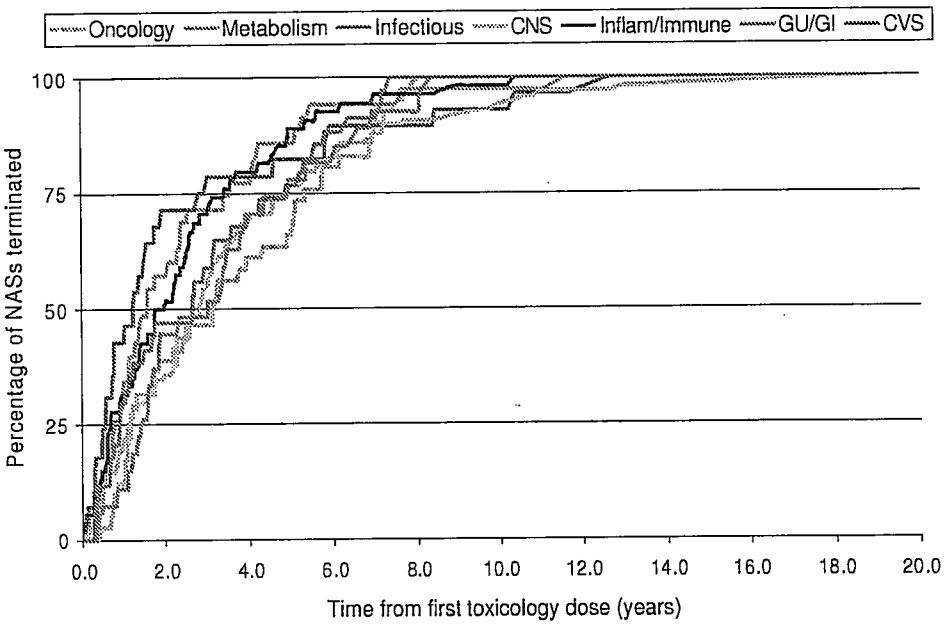


2.21 NASs per year per company

Source: CMR International | Unaudited data | Confidential | Slide No. 54

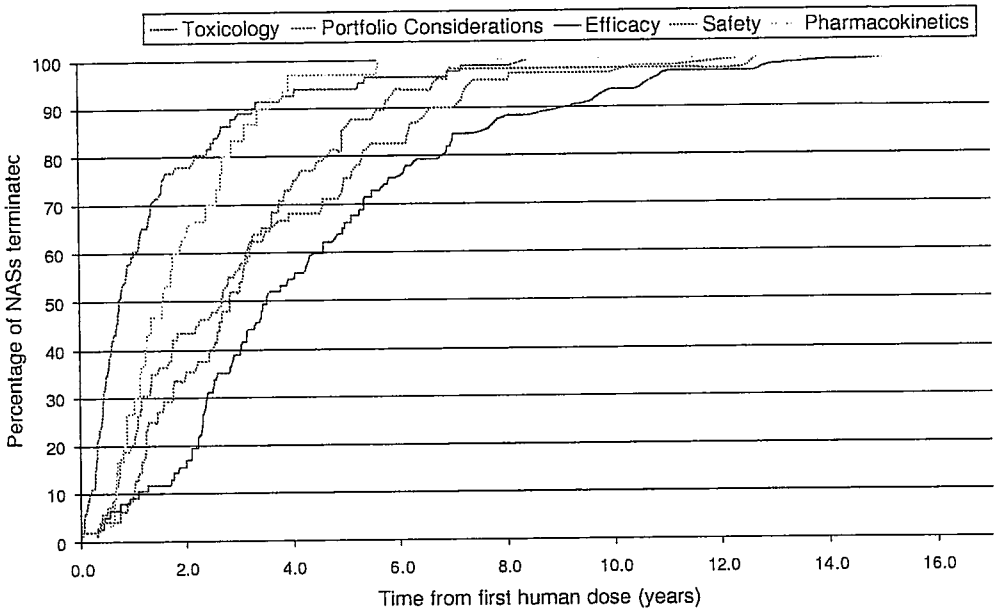
Part 3 – Focus on Terminations

Time to termination by therapeutic area



Source: CMR International Unaudited data *For NASs terminated between 1999 and 2001*

Time to termination by reason for termination



For NASs terminated between 1999 and 2001

Source: CMR International Unaudited data Confidential Slide No. 57

CMR International

Late Stage Terminations

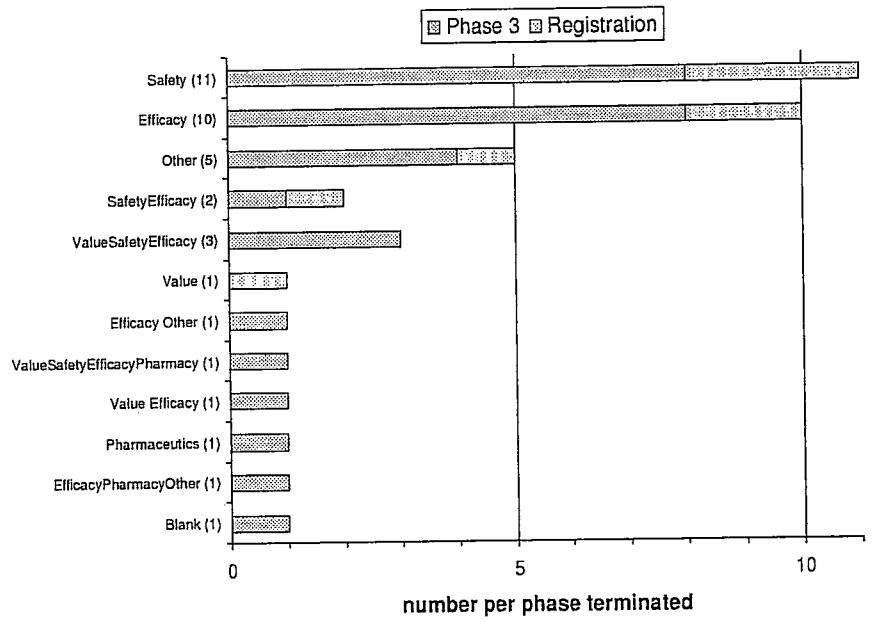
Short Sharp Survey June 2003

Terminations

- Prior to this Short Sharp Survey of late stage terminations CMR data has shown
  - majority of terminations in development are for clinical efficacy and portfolio reasons
  - in recent years portfolio reasons has been cited less frequently, efficacy remains high and clinical safety, very variable with a peak in 2000
  - companies reveal different profiles if the time to terminate is plotted for terminations,
    - the major companies tend to terminate after 2-3 yrs in development whereas in other this is around 3 years
  - Recent success rates are
    - 60% from phase III to submission
    - the probability of success is between 35 and 50% on entering Phase III

- The Late Stage Termination survey provides more detail on the reasons for terminations, the decision process for termination and lessons learnt

What are the main reasons and combinations of reasons for termination?



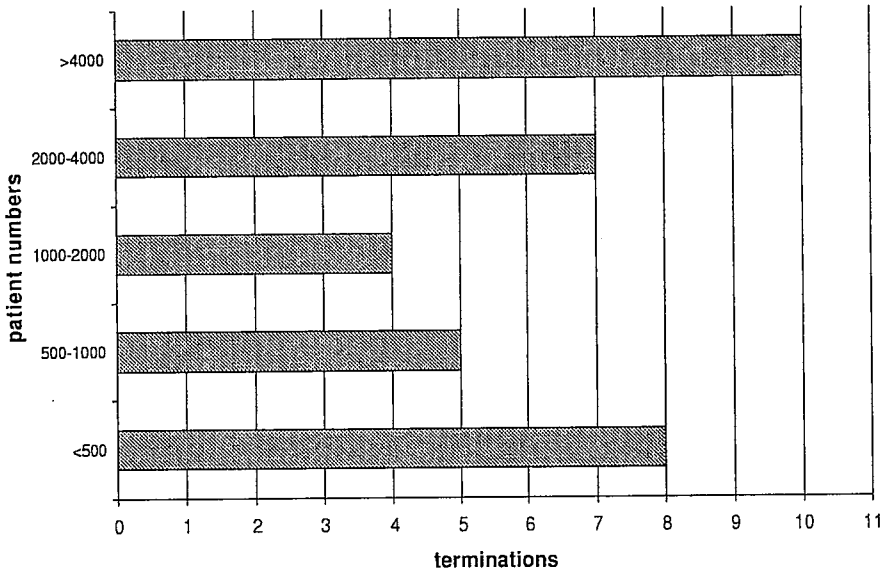
11 companies, 38 terminations

Source: CMR International | Unaudited data | Confidential | Slide No. 60

Highly Confidential

ABBT308643

For how many terminations were large studies undertaken?



11 companies, 34 terminations
4 terminations with no patient numbers

Source: CMR International Unaudited data Confidential Slide No 61

Highly Confidential

ABBT308644

Lessons Learnt

CMR International
Perspective ● Insight ● Opinion

- **Scientific findings**
  - "Carc" finding not determined without completing "carc" studies. Invitro mitochondirial studies that are now available might help but are not necessary predictive
  - Incidence of side effects in Phase II trial was acceptable but was higher than Phase III, small difference in incidence between phases.
  - not a forseeable problem
- **Thorough research**
  - must be an exhaustive and continuing search of patents in biologics area(due diligence);
  - earlier recognition of *weak signals and search for causes*
- **Approach to development**
  - better preclinical modelling for this disease target, better animal model for human toxicity, more invitro metabolic studies prior to nomination could have detected the effect
  - better identification of target patient population (high responders);
  - more dose ranging in phase 2, separation of Phase 2b and III
  - minimal info on mechanism of action so that dose selection and trial design was empirical; clinical candidate was toxic but selection of optimised candidate was not possible since *MOA was not known*; do not proceed with candidate for which MOA is poorly characterised and preclinical proof of principle is not reproducible
  - a study of manufacturing scale up earlier could have prevented this
- **Management & Decision making**
  - team had a back up cpd which made the decision easier
  - NCE championed through development by clinical in absence of commercial buy-in; proceeded to phase III without commercial assessment
- **Communication/relationships**
  - less optimistic partner
  - reviewed previous approval and summary basis of approval earlier, listened to the FDA reviewer of that submission,
  - prior agreement by FDA for use of imaging in clinical trials; more opinion leader/consultant for imaging technology and for patient selection